CLINICAL ENDOCRINOLOGY AND CONSTITUTIONAL MEDICINE

A.P. CAWADIAS, O.B.E., M.D., F.R.C.P.

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by

A. P. CAWADIAS, O.B.E., M.D., F.R.C.P.
ENDOCRINOLOGIST TO THE ORDER OF ST. JOHN CLINIC

"Medicine is now in a transitional phase. The ineptitude of regarding a man as a mere collection of interesting organs is becoming increasingly clear. The personality of their possessor is more important than his organs no matter what fascinating pathological condition or secretory versatility they may disclose."

R. G. HOSKINS.

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PREFACE

IN this work I have attempted to describe that new and fascinating branch of medicine, endocrinology, from the point of view of Clinical Science. This latter term is used in its historical sense as synonymous with nosology.

Medicine is an Art but needs for its practice the scientific knowledge embodied in two sciences or groups of sciences, Physiology and Clinical Science or Nosology.

Physiology, taken in its widest interpretation to mean Physio-Pathology, studies the functions of the body, the deviations of these functions from normal, and the various agents which act on these normal or abnormal functions. It thus includes Physiology (in the narrow sense of this term), Pathology, and Pharmacology. Its method is *à priori* reasoning, experimentation to control or develop hypotheses, and reasoning on the basis of experimentation for the discovery of general principles regarding the functions of the body and their abnormalities.

Clinical Science or Nosology studies the morbid phenomena as they manifest themselves in patients. It studies the form they assume, that is, the symptoms, the etiological factors which have caused them, the mechanism of the disturbance of body function which are at the basis of these symptoms, and the action of various therapeutic agents on these morbid phenomena. Its method is clinical observation (in the wide significance of the term, thus including the observation of symptoms, physical signs, modification of body chemistry and anatomical lesions), and reasoning on the basis of this observation to discover methods of diagnosing and treating the abnormal manifestations. In reasoning on the basis of his observations the clinician needs help from the facts discovered by physiology.

From its beginnings with Hippocrates, the Coan and the Cnidian physicians of the fifth century B.C., clinical science has adopted the nosographical method as a general procedure. As the Coan and Cnidian physicians had remarked that certain symptoms appeared in patients with a certain regularity of combination and evolution, they abstracted these combinations of symptoms from individual patients and constructed units of classification, fictional species, which are "diseases." This classification brought order into the immense variety of symptoms as exhibited by individual patients and provided a basis of scientific study, because classification is the basis of science. Thomas Sydenham, the great exponent of the nosographical method, showed that progress in medical knowledge consisted in completion of the natural history of "diseases," a natural history comprising four chapters, the clinical, the etiological, the physiopathological and the therapeutic. Succeeding centuries have developed these four chapters, and Sydenham's insistence on the neces-

sity of nosography for progress in medical science and thus in medical Art has been completely demonstrated.

The first Greek clinical scientists, principally Hippocrates, pointed out that diseases were artificial constructions and that physicians in the practice of their Art deal with individual patients and not with diseases. But they showed also that without knowledge of morbid phenomena the individual patient cannot be approached, and that the only method of acquiring clear knowledge of morbid phenomena is to study them on the basis of their nosographical classification, their natural history. Diseases are our working tools.

In the practice of his Art the physician needs both Physiology and Clinical Science. He cannot practise on the basis of Physiology alone; this has been attempted but with disastrous results. He needs Clinical Science, which in fact has a more direct bearing on practice, and is the science of practising physicians. Clinical Science, however, needs Physiology, otherwise it becomes a crass and useless empiricism. It needs physiology as physics needs mathematics, but, like physics and mathematics, Clinical Science and Physiology are separate sciences although often interwoven.

The late Sir Thomas Lewis, who did so much to bring Clinical Science to the forefront, unfortunately over-emphasised the physiopathological chapter of diseases and under-rated the great importance of clinical observation, omitting to point out that clinical observation is as scientific a method of investigation as experimentation, although of course much more difficult. I take the meaning of Clinical Science, as shown by history, as synonymous with Nosology. This was the definition of Clinical Science given by James Paget many years before Lewis. Clinical Science is the Natural History of diseases in their clinical, etiological, physiopathological and therapeutic chapters. The basic method is clinical observation in its wide sense. For the physiopathological chapter the clinical scientist or clinician needs to consider the results of the experimentation of the physiologist. The clinician experiments in certain cases of his patients, as when he performs functional tests or observes the action of drug administration. But *his* method is clinical observation. Experimentation is a method of the physiologist. The methods differ in parallel with the difference between the two sciences and the aptitudes needed for each.

It is from the point of view of Clinical Science that I have attempted to describe Endocrinology in this work. Instead of considering first the endocrine physiology and physiopathology and endeavouring to fit endocrine physiopathological disturbances into clinical pictures, I have first considered definite clinical or clinico-anatomical pictures and endeavoured to explain them on the basis of the findings of endocrine physiology and physiopathology. I have thus followed for Endocrinology the method which has effected progress in medicine since Sydenham, more particularly the method of the British and French clinico-anatomical schools. A precise endocrine nosography on these lines, as introduced by Addison, Gull, Pierre Marie, Harvey Cushing and many other clinicians will make for progress in endocrinology

in the same manner as a precise nosography has contributed to progress in other branches of medicine.

The difficulty inherent in a Clinical Science of endocrinology is the isolation of endocrine diseases. Diseases in other branches of medicine are isolatd on the basis of their clinico-anatomical chapters or, as in infectious diseases, on the basis of their specific etiology. In endocrinology we have to isolate diseases on the basis of their clinical pictures connected with a particular physiopathological disturbance. The difficulty is that whereas a clinico-anatomical picture is permanent, the conception of a physiopathological disturbance changes with the changing physiological conceptions. For this reason I have laid more stress in my classification on the clinical picture aspect, and have used mainly a clinical terminology, often employing the name of the clinician who first described the clinical picture. Personal names for diseases are justified in clinical science. In the first place, provided such names are historically accurate, it is good to bear in mind those who have helped in the progress of our science and art. Furthermore, personal names do not imply the particular physiopathology attaching to physiopathological names, and are thus of more permanent value.

Clinical Science needs Physio-Pathology, and the endocrinological branch of Clinical Science needs it more than any other branch. In fact, the therapeutic chapter of the natural history of endocrine diseases depends mainly on physiology. I have given a physiological introduction in which I have adopted the ideas which seem to me to conform best with the facts observed in clinical practice. I have emphasised the point that what we call endocrine diseases are in fact disturbances of an entire system of constitutional or metabolic regulation but predominantly of the endocrine component. Endocrine diseases include the majority of diseases of metabolism, Physiology as well as Clinical Science showing in fact that the specialty of endocrinology should be considered not only as the specialty of diseases of the five classical endocrine glands but also as the specialty of all metabolic diseases and those designated as constitutional diseases. The core of this specialty, however, is the study of diseases classified according to the predominant disturbance of the classical endocrine glands.

For didactic purposes I have placed the physiopathological chapter in the Natural History of endocrine diseases before the clinical descriptive chapter and have often united it with the etiological chapter.

In the last two chapters, abandoning the nosographical standpoint, I have tried hard to show how, on the basis of knowledge of endocrine and metabolic disturbances acquired by the nosographical method, the physician can approach his patient with the constitutional outlook. Modern medicine is permeated by this outlook. It is the passage from Science to Art.

My plan has been ambitious, and although I have studied this aspect of internal medicine ever since I worked as assistant to Professor Albert Robin of Paris I would not have ventured to publish the result of my work had I

not recognised the necessity for even such a small and incomplete contribution to constitutional medicine.

In accordance with the spirit in which this book was written I have used only a few composite pictures instead of photographs. My object has been to help the student and the physician to interpret the photographs of endocrine cases, which abound in many publications, on the basis of my composite pictures.

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January, 1947.

PHYSIOLOGY AND PATHOLOGY OF THE NEURO-ENDOCRINE SYSTEM

CHAPTER I

THE HISTORICAL DEVELOPMENT OF ENDOCRINOLOGY

Endocrinology is a branch of the science of medicine, and every science has to be described not only didactically but also historically. The didactic description consists in giving the conceptions of science as accepted to-day. The historical description consists in a review of the progressive development of our contemporary conceptions. Without history science becomes dead and stereotyped, and although it can be learnt it cannot be understood. This delineation of the history of endocrinology is not, therefore, a piece of literary work added as an ornament to the study of endocrine diseases, but is a necessary preliminary study which will enable the physician to "understand" this fascinating branch of our science. I shall describe the principal events in the development of endocrinological thought and practice, quoting only as illustrations some representative names.

Anatomical Description of the Major Endocrine Systems. The first stage in endocrinology was description of the classical endocrine glands. This began with the Greek physicians. It was developed in the sixteenth and seventeenth centuries by Vesalius, the Italian anatomists and the Oxford group of Thomas Willis, Thomas Wharton and Lower. It was completed in the nineteenth century by microscopical studies and the work is still continuing thanks to the introduction of microchemical methods in histology.

The liver and testis were of course known of old. The ovary was described first by Aristotle (fourth century B.C.) under the name Kapria. The term ovary was introduced by Niels Stensen (1648-86). Régnier de Graaf (1641-1673) started a more accurate description (Graafian follicle).

The thyroid was described first by Galen and re-described by Vesalius, who notwithstanding his vituperations against Galen copied him in many places, as pointed out by Daremberg. It was studied in particular by Thomas Wharton (1614-1673), who introduced the name by which the gland is known to-day. Its minute anatomy was first delineated by Lalouette in the middle of the eighteenth century but was made more complete in the middle of the nineteenth century by Bardleben, by Cruveilhier and by Virchow.

The pituitary also was described first by Galen and re-described by Vesalius. It was further studied by Thomas Wharton and Thomas Willis (1621-1675). Its structure was first delineated by A. H. Hannover (1814-1894) and developed principally through nearly contemporary work.

The adrenals were first mentioned by Galen (second century A.D.), according to Goldzieher, but principally by Bartholomeus Eustachius (1514-1564), the anatomist rival of Andreas Vesalius. John Riolan the younger (1580-1657) introduced the term suprarenal capsules. The first histological work dates from Ecker (1816-1887) and J. Arnold (1866).

The pineal gland was described first by Galen under a Greek term signifying " small pine cone." Its anatomical study was developed by Thomas Willis and Thomas Wharton.

The thymus was described first by Ruphas of Ephesus in the first century of our era. The endocrine pancreas, in other words the islet tissue, was described by Langerhans in 1869. The parathyroids were the last of the endocrine glands to be described, and were discovered by Victor Sandström of Upsala in 1880. Work is now proceeding on histological lines thanks to the introduction of microchemical and experimental methods in histology, which link structure with physiology. Further progress is expected with the development of new techniques in the use of the electron microscope.

Demonstration of the Internal Secretory Functions of the Endocrine Glands. The internal secretory functions of the endocrine glands were demonstrated long after the discovery of the glands themselves. Although Hippocrates and Aretaios connected virility with the seminal secretion of the testicle, and Aristotle described the constitutional effects of ovarian castration, physiological conceptions regarding these glands were for a long time speculative and erroneous.

Thomas Willis was the first to give an inkling of incretory functions, writing of the testicle : " The blood pours out something through the spermatic arteries to the genitals, so also it receives as a recompense a certain ferment from these parts—to wit, certain particles imbued with a seminal tincture are carried back to the bloody mass which make it vigorous and inspire into it a new and lively virtue " (Cerebri Anatome, London, 1664). Richard Lower (1631-1691) gave a similar inkling regarding a secretion into the blood from the pituitary. Thomas Ruysh (1638-1731) advocated a similar conception regarding the thyroid. Théophile de Bordeu (1722-1776) developed more completely the conception of internal secretions of the testis.

A new era began with John Hunter (1728-1793), who introduced his special method combining experimentation, comparative physiology and and anatomy, and clinical observation. He was the first experimental endocrinologist, and his experiments on gonadectomy combined with his comparative zoological work demonstrated distinctly the influence of the gonads on the sexual characters (which he was the first to analyse). In 1827, Astley Cooper performed the first experiments in thyroidectomy. Thanks to this impetus the conception of internal secretions developed and was accepted by T. W. King, of Guy's Hospital, in 1836, for the thyroid, by George Gulliver, one of the original Fellows of the Royal College of Surgeons, for the adrenals (1846), and by John Simon, of King's College Hospital, for the thyroid again (1844). Thanks to this work, the conception of the internal secretory functions of certain glands entered into the general domain of science, as is evident from the descriptions in the treatises on physiology of Johannes Muller in the eighteen-thirties, and of Jacob Henle (1841). Later, in 1846, Berthold, of Göttingen, gave a further demonstration of the internal secretion of the testis by repeating and developing John Hunter's experiments and by intrpreting these experi-

mental finding in the light of the already accepted and experimentally demonstrated doctrine of internal secretions. This brief outline shows that the role assigned to Berthold in German treatises as the " founder " of experimental endocrinology and the " originator " of the doctrine of internal secretions is not founded on fact.

The experimental demonstration of the doctrine of internal secretions was crowned in 1855, the peak of the history of endocrinology (Dana) by the work of Claude Bernard, Thomas Addison and Brown-Sequard. In his famous lectures at the Collège de France, Claude Bernard established the doctrine of internal secretions on the basis of his experiments on the liver. He maintained the existence of glands possessing both an external and internal secretion—the hæmopoietic organs, spleen, thymus, lymphatic glands, thyroid, suprarenals. He considered that these endocrine glands controlled the " internal environment," and with an intuition of genius ascribed the control of the internal and external secretions of the liver to the nervous system. In the same year, Thomas Addison published his monograph " On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," in which he gave the clinical, thus the highest, demonstration of the endocrine conception. One year later Brown-Sequard performed the first experiments in adrenalectomy.

Introduction of Endocrine Nosography and Pathology. Perfecting of Endocrine Physiology. The line given by this great triumvirate of endocrinology was the clinical study of the effects of disturbance of the endocrine glands and the experimental elaboration of problems raised by the clinicians. It was an enlargement of the Hunterian method, and for many years diseases of the endocrine glands were isolated and studied, and the impetus given by the clinicians resulted in a more detailed and exact study of endocrine physiology.

Although Hippocrates had already described male eunuchoidism and also a condition known to-day as Cushing's disease, Théophile de Bordeu had described male and female eunuchoidism, and Parry and Graves (1835) the endocrine disease known by their names, the endocrine basis of these disturbances was not well understood. Addison's disease can be considered as the first real endocrine disease to be described, and the fact that Brown-Sequard rushed into the laboratory to elucidate the problems raised by Addison's anatomo-clinical work shows the direction of subsequent work.

The first thyroid disease, known to-day as congenital hypothyroidism or congenital myxœdema, was described by Charles Hilton Fagge in 1871, and in 1873, William Gull described the acquired hypothyroidism of the adult. From 1881 to 1883 the two Reverdins, of Geneva, and T. Kocher, of Berne, established cachexia strumipriva (post-operatory myxœdema). All these clinicians linked the diseases they described with thyroid disturbance, but experimentation lagged behind. The first thyroidectomies of Astley Cooper and of Moritz Schiff (1856) had yielded no definite result, but after the clinical work mentioned, Schiff repeated his thyroidectomies in 1884, this time with definite results, and since then clinic and laboratory have worked together to

elucidate the thyroid physiology. It would be tedious to repeat for all the other endocrines what has been delineated for the thyroid. Scientific development continued on the same lines, isolation and dscription of new endocrine diseases stimulating further physiological work, medical progress emerging from the interaction of clinic and laboratory as codified in Claude Bernard's famous "Introduction to Experimental Medicine." One of the outstanding directives of physiological research originated in clinical therapeutic deavours. At the meeting of the Biological Society of Paris on June 1, 1889, Brown-Sequard reported the first therapeutic trial of a testicular extract, and in 1890, G. K. Murray, of Newcastle (later of Manchester), introduced thyroid extract injections for the treatment of myxœdema. This stimulated the extraction and study of the active endocrine secretions. In 1903, Bayliss and Starling developed the conception of "hormones," a term which they introduced into medicine, that is, of substances which are sent to the blood as chemical messengers to regulate the functions of organs and cells distant from the site of their production. The first hormone to be isolated was adrenalin, in 1901, zy Takamine, and independently, by Aldrich. Then came thyroxin (now considered as the nucleus of a hormone) by Kendall, and, as probably the most outstanding discovery, insulin, by Banting and Best. America entered the lists and with enormous vitality and material power succeeded in the isolation of other hormones. Stockard and Papanicolaou introduced a method for assay of the female hormones. Allen isolated œstrin, Koch testosterone, to quote only a few names.

Not only were hormones isolated and their chemical formulæ determined, but also their synthesis became possible. The old dream of the alchemists came true. Organic chemists do not prepare gold in their crucibles but something more valuable. They prepare these powerful biological agents which control the chemistry of the living body and thus life itself.

Enlargement of the Conception of Internal Secretions and Integration of the Endocrine System through the Hypothalamus and the Pituitary. In a new phase of medical work the conception of internal secretions widened. It was demonstrated as no longer limited to the major endocrine organs but regarded as a general cellular function. This view originated in the eighteenth century with Théophile de Bordeu and was developed in the nineteenth century by Brown-Sequard and by d'Arsonval, according to whom every tissue and body cell gives off products into the blood which influence other parts of the body. The extra-cellular enzymes became akin to the hormones. Certain cells isolated in various tissues, however, possess this power to a higher degree, such as some elements in the hypothalamus. A forward step in specialisation of internal secretion is represented by somewhat loose groups of endocrine cells constituting diffuse endocrine organs. The complete endocrine glands represent the final stage of specialisation. Needham and Waddington have shown that the cellular groups of the embryo constituting the organisers are minute morphogenetic endocrine organs.

All these endocrine organs were considered as loosely scattered in the body,

but a new line of research demonstrated their integration through the pituitary and hypothalamus. Harvey Cushing—and in England, Sir Walter Langdon Brown—have shown that the major endocrine system is integrated through the pituitary, which becomes its centre, the leader of the endocrine orchestra. But endocrinological thought goes forward. Roussy, of Paris, and his collaborators, have shown the diencephalo-pituitary connections. Cannon, in America, has developed the influence of the nervous system on hormonal secretions. It is thus shown that the hypothalamus and in general the brain is the centre of the endocrine system. The endocrine system, thanks to the work of T. R. Elliott (1904), of Cannon (1931), of Dixon (1906), and of Dale (1929), becomes part of the extended nervous system, and the nervous functions in general are shown to be neuro-hormonal functions.

Merging of Endocrinology with Metabolism and Constitutional Medicine. The contemporary step in endocrinological thought consists in the integration of endocrinology with metabolism and constitutional medicine.

William Prout, in 1813, began to lecture on animal chemistry as applied to medicine. Albert Robin, in the early 'seventies, developed the conception that disturbances in the biochemistry of the body, disturbances of metabolism as we say to-day, precede organic localisation in disease and thus directed the attention of physicians to these disturbances. In this view originated the medical branch of metabolism, subsequently developed by Charles Bouchard, Archibald Garrod, Friederich Muller, Carl von Noorden, and others. The metabolic or biochemical processes of the body, however, were shown to be regulated by the endocrine glands and the liver, which is considred as part of the endocrine system. Thus endocrinology was integrated into the wider conception of metabolism and profited from the great discoveries of biochemistry.

In the meantime, another medical movement, the Neohippocratic movement, beginning after the first world war, attracted the attention of physicians, who in the sway of organic conceptions and of the cellular theory had lost their view of the " whole man," of the environment of the " whole man," of the " constitution." Constitution, however, the whole psychophysical structure of the individual, has been shown to depend on the physiochemical processes of the body, on metabolism. This metabolism is further demonstrated as controlled not only by the endocrines but also by the genes, the organisers, the vegetative nervous system and environmental, mainly nutritive, factors (vitamins). The endocrines have become part of the system of constitutional or metabolic regulation, and endocrinology (and metabolism) have merged into the wider conception of constitutional medicine.

Thus the endocrinologist of to-day considers not only the six or seven classical endocrine glands but is predominantly a metabolic physician, a constitutionalist, although the classical endocrinology constitutes the precise basis of his work.

CHAPTER II

CONSTITUTIONAL METABOLIC REGULATION AND THE ENDOCRINE SYSTEM

Constitutional medicine is the study in health and disease of the system of constitutional regulation, a system composed of genes, organisers, endocrines, nervous vegetative system, psychoassociational cortex, nutritive and other environmental regulators, and a group of other regulatory factors designated " competence." From the nosographical point of view the objects of study of the internist-constitutionalist are those diseases which show as preponderant element a disturbance of the constitutional regulatory system.

Endocrinology is the study in health and disease of the endocrine system, one of the components of the system of constitutional regulation, and from the nosographical point of view is the study of diseases showing predominance of endocrine disturbances.

As the system of constitutional regulation functions as a balanced system which changes as a whole when any one of its factors alters, endocrinology can be studied and practised only within the frame of the whole system of constitutional regulation and is thus one part, one aspect, of constitutional medicine.

Constitutional medicine and thus endocrinology can be understood only if the term " constitution " is defined with precision. Let it be said at once that constitution is not, as Tandler and Martius and Julius Bauer understand it, merely the hereditary features of the individual, Johansen's genotype. This concept is erroneous from the standpoint of pure science, because hereditary cannot be separated from acquired features in an individual, but all features result from an interplay of hereditary and acquired factors. It is also wrong pragmatically, for as often happens with inadequate terms which fossilise our concepts, it has greatly hindered work on the understanding of constitution and has been the source of unjustified therapeutic nihilism regarding constitutional diseases.

The constitution of an individual is the sum total of his features, both hereditary and acquired. It is Johansen's phænotype, the whole psycho-physical structure of the individual. However, to say that constitution is the whole psycho-physical structure of the individual is simply to interpret one term by another. There has been sufficient work of recent years, beginning with the ideas of the Neohippocratists and crowned by the work of endocrinologists and biochemists, to allow of a genuine definition, thus a genuine understanding of constitution.

Life is a chemical function. These words, pronounced by Lavoisier a little over a hundred years ago, dominate contemporary medical conceptions. Life is utilisation of oxygen, proteins, fats, carbohydrates, minerals. Life is thus metabolism, to use the term introduced by Schwann. Constitution, which is a unit of life, is thus a matter of chemistry, of metabolism, and metabolism is regulated by a complex system to be designated as system of metabolic or constitutional regulation. This system is composed of the neuro-chemical induc-

tors, genes, organisers, of the neuro-endocrine and neuro-vegetative systems, the psychoassociational cortex, the nutritive and other environmental regulators, and those forces, still mysterious, which are designated as competence. The constitution, the psycho-physical structure, of an individual is thus his mode of utilisation of oxygen, proteins, fats, carbohydrates and minerals, in other words, the mode of function of his system of constitutional regulation.

The system of constitutional regulation should be understood not as a system of organs, although for descriptive purposes it is here analysed into organic components, but as a system of forces. In constitutional medicine thought proceeds in terms of dynamics, not in those of anatomy or even of the usual physiology. We must think in terms of balance of forces, Alkmeon's Ισονομια and thus, in pathological conditions, in terms of rupture of a whole balance placing the entire system momentarily under the sway of one of its dynamic components, Alkmeon's Μοναρχια, and not in terms of localised disturbance of one or more organs. Pathology in constitutional medicine and endocrinology is a pathology of regulation and correlation, not of organ deficiencies.

THE COMPONENTS OF THE SYSTEM OF CONSTITUTIONAL REGULATION

The Chemical Inductors, Genes, Organisers, Neuro-Endocrine System. The chemical inductors constitute the first group of forces to be considered in constitutional regulation.

The genes are the first chemical inductors to appear in ontogenic evolution. They act by secreting ferments or enzymes (Goldschmidt, J. B. Haldane) which regulate intracellular metabolism. They are responsible for certain metabolic functions which give a permanent character to certain cells. For instance, there is a gene responsible for depositing pigment in the cells of the iris. Some genes make these cells contain only blue pigment, which is possessed by all normal eyes except those of albinos, and for this reason the eyes of all humans are blue for the first few days of life. Later this same gene in some cases makes the cells deposit brown pigment, which is laid in front of the blue and obscures it, and the eye appears brown. The rate of deposition of the brown pigment and the time of its appearance are responsible for differences in eye colour. There are genes that direct cellular metabolism only towards deposition of blue pigment, others that direct it also towards deposition of brown. Why this gene, which starts in the fertilised ovum, becomes manifest only in the development of the cells of the iris, we do not know, but it is certain that the metabolic function resulting in the particular pigmentation of the iris is regulated by a gene and not by an endocrine gland, as are other metabolic functions.

This is an example of a simple metabolic regulation due to a gene, but a single gene may regulate metabolism in such a manner as to have multiple effects, and disturbance of this gene results in disturbances of metabolism with multiple effects. For example, a single abnormal gene will give rise to an

abnormal metabolism of the sclerotics and bones simultaneously, and will be responsible for fragilitas ossium, a disease characterised both by blue sclerotics and bone fragility. A single gene gives rise to the Laurence-Moon-Biedl syndrome, the features of which are obesity, hypogenitalism, polydactyly, retinal degeneration and mental deficiency.

In this first or genetic stage of metabolic regulation is apparent the general law of metabolic regulation that a balance of forces, not a single factor, regulates metabolism. The genes form a system, a complex, and everything depends not on one gene but on the balance of the genetic system. It is impossible to alter a single gene without modifying many others. The effects of a single gene will be changed if it is placed in a different gene complex. In the Mexican Top minnow a gene Sp merely produces black spotting. If this gene is transmitted to a hybrid between the Mexican Top minnow and another genus, the Swordtail (which of course contains a gene complex different from that of the Top minnow) it gives rise to a fatal cancerous growth. A gene (not sex linked) that produces a certain character in a female, for example, Steatopygia, will not produce the same character in a male, *i.e.,* in a different gene complex.

The action of the genes shows the same principle as that of the endocrines. Metabolism, life, development, are the result of the interaction of three series of forces, a genic-organiser-endocrine impulse, a biological field, a special environment. The term environment is clear, but " biological field " requires some explanation. Its conception is derived from that of the magnetic field, and it denotes in terms of energetics a morphological and pre-morphological domain actively organising itself. It represents in terms of energetics an aspect of the developing human being, the unicellular organism as well as the embryonic mass. It is a real entity, a system of forces that can be isolated in the living being. The concept of the biological field, developed mainly through the work of Joseph Needham and of Charles Waddington, is penetrating slowly into medical thought in measure with the habit of thinking not only in terms of material localisation but also in those of dynamics, of lines of force. The field has potentialities of self-differentiation. The metabolic regulation effected by the genes depends on the interaction of a special genetic impulse (incretion of a genic ferment), of a particular reactivity and competence of the field, and of a special influence on both by the environment. This same principle applies to endocrine action in general.

Genes direct metabolism through their primary action, and are the sole regulators of metabolism in the first phases of embryonic life and in certain lower animals. Later in development or higher in the animal scale, genes direct metabolism also by instituting special executives, the organisers, and later, through the organisers, the endocrines.

The organisers. These constitute the second group of chemical inductors appearing in the course of development of the human being. They depend for their development on the genes for the particular organisers, normal genes giving normal organisers and hereditarily abnormal or mutated genes producing abnormal organiser systems.

The primary organiser (Speemann's organisator), studied particularly in the amphibian embryo, appears at a very early stage, probably before cleavage starts. It is in the region of the dorsal lip of the blastopore. If a piece of this region is grafted into another embryo in the blastula or early gastrula stage it will " induce " the neighbouring host to form a secondary embryo, often including nerve tube, brain, eyes, somites, notochord. Besides the central organiser, and probably through its influence, secondary organisers develop.

General development depends on the organiser system. A piece of ectoderm is determined first of all by the primary organiser to form head ectoderm, next it is determined by the secondary organiser of the eye cup to form the lens of the eye, and so on. In the absence of the organiser normal development and differentiation do not occur.

Induction of development from the organiser results, as the researches of Speeman and in particular of Needham have shown, from a hormonal secretion. The chemical nature of this organiser hormone has been studied and found to be of fatty, lipoidal or sterolic nature, and thus related to the sterols whose nucleus constitutes also the sex hormones, the cancer-producing substances, and vitamin D. This organiser hormone is a morphogenetic hormone. It is the first sterol to appear in the economy. It acts in the same manner as the definite hormones. According to Balinsky, the essential feature of the process of induction, which is determined by the inductor or morphogenetic hormone of the organiser, is the raising of metabolic activity in the tissue on which the organiser acts. The actual differentiation which occurs in the induced tissue is considered as a consequence of the elevated metabolic rate. Later, as will be seen, the thyroid hormone acts also by raising the metabolic activity of tissue, and the differentiation which occurs in the tissue subjected to thyroxin is a result of the elevated metabolic rate.

Study of the organiser system has made even clearer the concept of the biological field (or, in other terms, tissue competence, reactivity to incretions) a finding which has a parallel in the neuro-endocrine system. According to Needham: " In the determination of the main axis of an animal by an organiser, two processes or two aspects of the same process can be distinguished, (1) the determination that an embryonic axis shall be developed; (2) the determination of the character of the axis, *i.e.*, that one end shall be the head and the other the tail. It has been suggested that the former process be called evocation and the latter individuation." In a transplantation, evocation is always performed by the graft, individuation seems to be performed by the host and the graft working together either in a co-operative or in an antagonistic manner. Evocation can be regarded as of strictly hormonal character, individuation requires the intervention of a new concept, that of " biological field " by analogy with the magnetic field. Clinically we would speak of special tissue reactivity.

The organisers direct differentiation of the primitive uniform cellular mass (the blastula and gastrula) into particular tissues and organs. Thus one organiser directs the development of one part of the embryonic mass into

nervous system, another guides the development of another part into a limb, an endocrine, and so on. There are primary, secondary and tertiary organisers.

The neuro-endocrine system. This system comprises a third series of chemical inductors. In ontogenetic development they come after the organisers. They represent a wider and more definite function of metabolic and thus of constitutional regulation.

Endocrine function is a function of all cells, and thus exists from the beginning of development. Progressively, however, certain cells specialise in internal secretion, these unicellular endocrine organs existing even in the adult, *e.g.*, in the hypothalamus and spinal cord. Such incretory cells may collect together without forming a separate organ, but existing more or less scattered in the tissues. They then constitute diffuse endocrine organs, exemplified by Masson's argentaffine organ scattered in the mucous membrane of the gastrointestinal tract and by a similar diffuse cellular formation spread in the duodenal papillæ and probably secreting the hormone secretin. Finally come the endocrine glands, which are more definite and limited collections of incretory cells constituting glandular formations whose secretions pass into the blood flowing abundantly through them.

These endocrines appear after the nervous system. In the seventh week the cells of the anterior lobe of the hypophysis begin to differentiate into a glandular type of cell. In the eighth week the thyroid, at first connected with the digestive tube, differentiates as an endocrine organ. At the same time the gonads, already in existence as an undifferentiated genital ridge, differentiate as endocrines. Progressively there appear the pancreas, adrenals, thymus and parathyroids.

At a later stage occurs the union of nervous system and endocrine organs. Progress in evolution, phylogenetic as well as ontogenetic, consists in intimate correlation for purposes of integration, which is effected ultimately through the brain. Endocrines are connected with the nervous system, and the endocrine system becomes the neuro-endocrine system and thus a part of the nervous system.

A general delineation of the nervous system shows the place of the endocrines in the economy of the body.

The nervous system possesses an afferent section, the sensory system, through which the body-mind receives external stimuli, information as to the environment. Sensory impulses are transmitted to various centres, ultimately reaching the thalamus, sensory cortex and the psychoassociational cortex, where they are elaborated. In any of these centres afferent stimuli are transformed into efferent or motor impulses for regulation of the entire body-mind, impulses regulating movements and behaviour through the neuro-muscular part of the efferent nervous system, impulses regulating visceral function through the neuro-visceral system which comprises the greater part of what is known as the vegetative system (designated here as neuro-vegetative system), impulses regulating the chemical processes and constitution of the body through the neuro-metabolic system.

All these efferent or motor impulses are neuro-chemical. Muscular movement is the result of a nervous impulse terminating in the production of a chemical substance, the hormone acetylcholine. Modification of visceral function is the result of a nervous impulse, transmitted through vegetative nerves and ending in production of an adrenilergic or cholinergic hormone. Modification or regulation of metabolism is the result of a nervous impulse transmitted through certain vegetative nerves and terminating in the production of a hormone. The difference here is that whereas for muscular movement and visceral function a limited action is necessary and the hormonal element is small and localised, for metabolic changes a more diffuse action is necessary and thus the chemical or hormonal element has greatly developed through formation of special organs to which the nervous impulse is transmitted, the endocrine glands. This development of the terminal hormonal element in the neuro-metabolic system is so great that the endocrine glands may acquire a certain degree of independence of the purely nervous impulse.

All three effector parts of the nervous system possess centres at different levels. The neuro-muscular system possesses centres in the telencephalon, diencephalon, metencephalon and spinal medulla. The neuro-visceral or neuro-vegetative system also possesses centres in the telencephalon, as demonstrated by Fulton, in the diencephalon, the metencephalon, the spinal medulla and in the vegetative ganglia. The neuro-endocrine system also possesses centres at all these levels, although their great centre is the diencephalon.

The centres of all three effector parts of the nervous system are activated by external stimuli, which reach them by a nervous afferent and a chemical afferent route. The nervous afferent stimuli or nervous messengers are purely nervous sensory or psychical (psychical messengers). The chemical afferent stimuli or chemical messengers consist in modifications of body fluids brought about by various factors such as intense respiration, heat, changes of internal metabolism. These chemical stimuli reach the various centres of the neuro-somatic, neuro-visceral and neuro-endocrine systems through the blood flowing through these centres.

The Neuro-Vegetative System. The neuro-vegetative system (autonomic system) participates in the system of forces regulating ionic equilibrium. It is intimately connected with the neuro-endocrine system and, like it, is centred in the hypothalamus. Through its direct action (which, however, is always neuro-hormonal as ultimately the nervous impulse induces secretion of an adrenalinergic or cholinergic hormone) it stimulates the metabolic functions of the cells or may modify the reactivity of the cells to other constitutional regulators—hormones, vitamins, environmental factors.

The Psychoassociational Cortex. The psyche, or in more biological terms the psychoassociational cortex, belongs to the system of constitutional or metabolic regulation. It is with some hesitation that an " organic physician " writes these words. During more than two hundred years positivism—in fact a false positivism—has become traditional. All psychological factors have been treated with contempt and dismissed as metaphysics, and these errors

and their tragic results have been made so violently manifest that they are now acknowledged barely and with hesitation. The psyche has been for many years the unpleasant truth from which the ostrich buries its head, but it must be faced.

The psychoassociational cortex is an organ, a superior organ. In it are collected and elaborated impressions, " stimuli," from the environment. From it depart various motor impulses which, through the hypothalamic centres of the neuro-vegetative and neuro-endocrine systems, regulate the chemistry of life and thus the functions of the whole organism, the " body-mind."

Recent neurological work on the architectonics of the cerebral cortex, so brilliantly summarised by Economo, helps to a more scientific understanding of the psychoassociational cortex. Its centre lies roughly in the frontal lobes, but is not an absolutely limited centre. Thus tactile stimuli are received approximately in the post-central gyrus (Brodman's area 1), more delicately elaborated in the intermediary post-central and parietal areas (Brodman's areas 2 and 7) and definitely elaborated into mental symbols in the frontal lobe. Visual stimuli are received in a visuo-sensory area of the occipital lobe, elaborated in the visuo-psychic area of the occipital lobe, and definitely elaborated into mental symbols in the psychoassociational areas. A similar course is taken by auditory stimuli through audito-sensory and audito-psychic areas in the temporal lobe. Motor impulses originate as definite symbols of the act to be accomplished in the psychoassociational cortex in the frontal lobe. They are analysed into complicated movements in the intermediary pre-central or psychomotor area (Brodman's area 6) which registers engrams and motor schemes, and further analysed into simpler movements in the pre-central or motor area (Brodman's area 4).

The functions of the psychoassociational cortex can be expressed in terms of mental phenomena, which serve to describe its structure.

The psychoassociational cortex is that area of the body in which the psychological personality (more usually and simply called the personality) gradually takes form. At birth it is not a clean slate but possesses certain engrams transmitted through heredity, the hereditary or collective subconscious (Jung). These are, however, the faintest rudiments of personality structure. Personality develops, as indicated by ancient philosophers, mainly the Stoics, through the action on the psychoassociational cortex of impressions from the exterior. This enters into the domain of philosophy, but general medical principles cannot be dissociated from philosophy. Zeno, Cleanthes and Chrysippus spoke of " soul " and held that personality was built up progressively by the various perceptions determined by environmental impressions. Lacking knowledge of the psychoassociational cortex they were at a loss to explain the action of objects on the " soul " but they regarded this action as grossly material, Zeno defining perception as an impression made on the soul and Chryssipus as a change (τυπωσις) made in the soul—or as it would be expressed to-day, in the psychoassociational cortex. Perception gave rise to memory, repeated acts of memory to experience, and conclusions based on experience determined

conceptions going beyond the sphere of direct sensation. Thus the development of the psyche was progressively completed.

However, sensations and perceptions, whether transmitted as engrams through heredity or acquired in the course of life, cannot build up a psychical personality any more than bricks and stones explain the building of a house. All perceptions must be integrated according to a special plan. This integration is a basic biological law. Unity is the basis of life. It exists already in the unicellular fertilised ovum and persists in the complex human being. This great truth was lost from sight so long as Virchow's erroneous conceptions prevailed, even though at the same time British biologists were insisting on this unity principle. On the basis of the fundamental principle of unity the system of constitutional regulation is constructed in an effort of the organism to maintain its unity in the complex body-mind. Also on the basis of this unity all perceptions, inherited as engrams or acquired, are integrated into personality.

The psychoassociational cortex is an important factor in the integration of the body-mind, but is not integration itself. The body-mind is integrated through a whole system of constitutional regulators, of forces, among which the psychoassociational cortex is important. It is true that because of its central and preponderant position the psychoassociational cortex appears " as if " it is the summit of integration, but it is only in this sense that it can be taken with Sherrington as the summit of integration.

On these notions is based the conception of psychosomatic medicine, which marks in medical art to-day a progress equal to that effected by the bacteriological discoveries of Pasteur seventy years ago. The psychosomatic principle must not be taken as the action of psyche on soma. This presupposes a duality in the human being rejected by most Greek philosophers and introduced only by the early Christians, a duality which does not in fact exist. In constitutional disturbances the whole system of constitutional regulation is out of balance. Emotional factors may cause the breakdown of this system at its psyche component, which may therefore colour the clinical manifestations of the imbalance; but disturbance of a system of forces at one place throws the entire system out of gear, and thus the other components of the constitutional regulatory system also are involved.

Thus endocrine disturbances following psychogenic upsets are not caused by a direct action of the disturbed psyche on the endocrines, but represent mainly the independent reaction of the endocrines in their endeavour to compensate the general imbalance of the system of constitutional regulation determined by its break at the psyche link. Similarly, psychological disturbances following endocrine dysfunctions are due not only to a direct action of the endocrine dysfunctions on the metabolism of the psychoassociational cortex, but also represent the independent reaction of the psyche in its effort to compensate the general imbalance of the system of constitutional regulation determined by its break at the endocrine link. Independent compensatory reactions, of the endocrines in the first instance, of the psyche in the second

instance, depend on the particular capacity of the endocrines or the psycho-associational cortex.

This point has been emphasised because the psychosomatic problem is approached much as some Byzantine theologians speculated as to whether the hen was created first and laid the first of all eggs or whether the egg was created first to hatch into the first of all hens. Constitutional medicine demands holistic thinking, which must proceed in terms of an entire regulatory system and abandon the simpler modes of thinking preponderant in other aspects of medicine. The splendid developments of recent years which have integrated psychiatry into internal and thus constitutional medicine must not lead us to replace one unilateral view by another, but should provide a more complete understanding of the pathology of correlations and regulations.[1]

Extrinsic Factors (Nutritional Factors, Vitamins, Meteorological Factors). *Nutritional Factors.* Nutrition is a metabolic and thus a constitional regulator. It is obvious that body chemistry depends on the food given to be metabolised. An abnormal diet cannot bring about normal chemical reactions. Further, the other constitutional regulators (endocrines, nervous system) depend for their normal function on an adequate and well-balanced intake of food, normal intake depending not only on normal supply but also on normal digestion, absorption and elimination through the intestines and kidneys.

The elements of food include factors with specific metabolic regulatory functions. Among these are the indispensable aminoacids such as tyrosin, which cannot be synthesised by the body from other elements and is absolutely necessary for normal production of adrenalin and thyroxin, and lysine, which is indispensable to growth. In fact growth, an important result of metabolism, and tissue differentiation depend greatly on certain aminoacids. Tadpoles have been reared on a diet adequate in carbohydrates, fats and vitamins but containing a single aminoacid as nitrogenous food, and it has been shown that arginin, cystin, lysine and phenylalanin permit growth but practically no differentiation, whereas tyrosin and tryptophan favour differentiation rather than growth, thus producing small but well developed animals. Leucine and alanin permitted neither growth nor differentiation. The fatty foods also include some indispensable fatty acids such as linoleic acid, which has even been termed vitamin F as its absence from diet causes important metabolic disturbances.

Vitamins. These form a special class among the indispensable nutritive factors entering into the system of constitutional or metabolic regulation. They act as co-enzymes in cellular oxidation, and in general have a direct regulatory action on certain cellular metabolic functions. They are indispensable in many cases for normal function of other constitutional regulators, particularly of certain endocrines. They are with some justification termed external hormones, and are even often akin to organiser inductors or evocators.

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(1) This is written from a biological, thus phænomenological, point of view. It does not interfere with a noumenal spiritual interpretation of the Universe.

Meteorological factors. The biological unit is the living being in its particular environment. The living being cannot be separated from its environment, as Hippocrates recognised. He called the environment the external constitution, and developed this idea in his masterpiece on airs, waters and places. In a more poetical but less scientific manner Paracelsus developed the idea of the macrocosm-environment acting on the microcosm-man.

Competence, Reactivity. Forces representing competence or reactivity join with chemical inductors, neuro-vegetative system, psyche and environmental factors to form the system of constitutional regulation. These forces have been described in the delineation of the biological field and in fact represent that field.

The term competence has been used principally by experimental embryologists (Needham, Waddington). It indicates the capacity of a part of the embryo to react to a given morphogenetic stimulus by determination and differentiation in a given direction. Competences appear in a succession at definite stages of development and later disappear, whether or not any of them have been implemented by the appropriate morphogenetic stimulus. The term competence can be maintained also for the reactivity of adult cells to hormones (including those representing the terminal effects of the nervous stimulus). The simpler term reactivity also can be used, but as it has a more general significance I prefer the term competence.

An analytical description of the system of constitutional regulation is artificial; a system of forces cannot be described in analytical terms as each component force depends on the whole system. Thus, description of the chemical inductors, genes, organisers, endocrines has entailed consideration of the competence (biological field) and the environmental forces. In the same manner, competence cannot be absolutely isolated. It depends on the whole system, as shown clinically and experimentally, on endocrines, neuro-vegetative system and environmental regulators.

GENERAL STRUCTURE OF THE NEURO-ENDOCRINE SYSTEM

This work deals with those constitutional diseases showing a preponderance of endocrine disturbance, with those imbalances of the system of constitutional regulation in which the breakdown occurred at the neuro-endocrine component.

The considerations in the preceding chapter show that the endocrines can no longer be regarded as separate organs, but must be connected with the nervous system as forming a part of the constitutional regulatory system. The " endocrine system " is really the neuro-endocrine system.

It is puzzling that endocrinologists in their description of the endocrine system make an artificial section at the slender but important pituitary stalk and begin by dealing with the pituitary. The pituitary and other endocrine glands are not, like the tomb of Mahomet suspended in the void. They form part of the nervous system, within which they are integrated.

The Hypothalamus. The keystone of the endocrine system, the conductor of the endocrine orchestra, is not, as usually stated in textbooks of

endocrinology, the pituitary, but the hypothalamus. The pituitary is only the major link uniting the nervous and hormonal components of the neuro-endocrine system. The hypothalamus works under the control of the superior cerebral centres, particularly of the cerebral cortex, but is itself the main centre for regulation of visceral function and body chemistry.

The hypothalamus is phylogenetically the most ancient part of the fore-brain because it is concerned with vegetative functions. It is a central neuro-glandular mechanism controlling the basic rhythms of organic life. In it functional mechanisms of the highest importance are crowded together in an astonishingly limited space. By the third month of fœtal life the forward or rostral end of the neural tube is divided from below upwards into three parts, the rhombencephalon, the mesencephalon, and the prosencephalon. The prosencephalon, at this time or slightly earlier, is divided into a posterior part, the diencephalon, containing the hypothalamus, and an anterior part, the telencephalon. The hypothalamic part of the diencephalon takes over the regulation of vegetative functions. The telencephalon develops for integration of all body functions and thus exerts some degree of control, mainly inhibitory, on the hypothalamus.

The hypothalamus constitutes mainly the floor of the third ventricle but extends slightly upwards and on each side of the ventricular cavity. It reaches from the level of the pre-optic region anteriorly to the caudal end of the mammillary body. Above the hypothalamus and separated from it by a groove is the thalamus. The hypothalamus is divided anteroposteriorly into three regions, pars supra-optica, tuber cinereum to which the hypophysis is attached, and pars mammillaris. It is deep at the base of the brain, hidden and protected by the large cerebral hemispheres and thus able to resist influences which over-power other regions of the brain. According to Miller it measures 14 mm. anteroposteriorly, 18 mm. from above downwards, and 10 mm. in width.

It is constituted mainly by a series of nuclei, most of them only a few millimetres in dimension and yet possessing potent and widely effective physiological properties. The principal among them are, from above downwards, (*a*) the pre-optic nuclei, which anatomically do not form part of the hypothalamus but are bound up with its function, (*b*) the nuclei of the supra-optic areas, the nucleus paraventricularis connected with carbohydrate metabolism, the nucleus supra-opticus connected with water metabolism, the nucleus supra-chiasmaticus, (*c*) the nuclei of the pars tuberalis hypothalami, (*d*) the nuclei of the pars mammillaris connected with sleep regulation, the most differentiated part of the hypothalamus in the higher mammals and receiving the fornix bundle from the hippocampus. This is only a delineation, and the structure of the hypothalamus should be thoroughly studied by the endocrinologist, for example, in the classical treatises of Miller, Le Gros Clark, Tilney and Riley.

To regulate visceral and metabolic functions the hypothalamus receives information as to the actual condition of these functions through various nervous and chemical messengers. The nervous messengers come from all sensory terminations and the sense organs through the thalamus and the

thalamo-hypothalamic connections. They come also from the cerebral cortex, and the cortico-hypothalamic afferent connections (fronto-hypothalamic tract, Vicq d'Azyr bundle, hippocampomammillary tract, medial forebrain bundle) are important as linking cortical and thus mental function with the hypothalamus. The chemical messengers consist in changes in the constitution of the blood flowing through the various hypothalamic nuclei.

These nervous and chemical sensations are transformed in the hypothalamic nuclei into motor impulses which, through the various efferent tracts arising from the hypothalamus, go to other parts of the nervous system, to the endocrines, to various tissues and organs. The efferent connections with the cortex (mammillothalamic tract, *e.g.*) are important in bringing the cortex and thus the whole individual integrated by the cerebral cortex into total activities arising from modifications of body chemistry or visceral function. They constitute an integral part of the process of telencephalisation. Other efferent tracts go to the inferior centres of the sympathetic and parasympathetic, influencing mainly visceral function. The efferent tracts of especial interest to the endocrinologist are those connected with endocrine functions.

The following are the most important.

1. *Hypothalamo-posthypophyseal tracts.* These are the best demonstrated. The most important is the supra-optic hypophyseal tract, which arises in the nucleus supra-opticus (and possibly from other nuclei), runs back to the side of the tuber cinereum and terminates in the posterior lobe and the pars media of the hypophysis. Through this tract the hypothalamus stimulates the post pituitary and mediopituitary secretory cells in their secretion of antidiuretin, oxytocin, vasopressin, intermedin, and possibly a fat-metabolic hormone.

2. *Hypothalamo-hypophyseal tract through the superior cervical ganglion.* From various hypothalamic nuclei (precise details are not known) a tract descends from the hypothalamus and terminates in the lateral horns, thus in the sympathetic centres of the spinal medulla in its first thoracic segment. There occurs the first synapse, and from the neurones of these horns emerge other fibres going to the superior cervical ganglion. There another synapse is formed, and from the cells of this ganglion emerge other fibres which follow the carotid plexus, terminating in part in the anterior lobe of the pituitary. Through this tract the nuclei of the hypothalamus stimulates secretion of all the endocrinotropins of the antepituitary (thyrotropin, parathyrotropin, *α* and *β* gonadotropins, adrenotropin) and the particular metabolic hormones of the antepituitary, growth hormone or phyone, diabetogenic hormone or diabetogenin, mammogenic hormone or prolactin or mammogenin, and possibly a fat-metabolic hormone and Collip's metabolic hormone.

3. *Hypothalamo-pancreatic tract.* From the caudal part of the nucleus paraventricularis arise fibres contributing to the formation of the fasciculus longitudinalis dorsalis of Schutz. Part of this descends to the vagal nucleus, where the first synapse occurs. From the dorsal vagal nucleus fibres following the vagus go to the pancreas, especially to the pancreatic insula. Urechia and

Nitescu have recorded degenerative changes in the paraventricular nucleus following puncture of the dorsal vagal nucleus and a similar degeneration, although less marked, after pancreatectomy.

4. *Hypothalamo-adrenal medullary tract.* This shall be described with the adrenalin system.

The Pituitary Gland. This is the great glandular link. Through it the central nervous system is connected with the other endocrines. It is not the keystone of the glandular system (that position is held by the hypothalamus), but the anatomical location of this gland, viewed in the light of the phylogenetic laws of centralisation, cephalisation, increased protection from trauma and direct alliance with the nervous system, shows its great importance.

The pituitary lies in the sella turcica, which is situated in the median portion of the middle cranial fossa above the body of the sphenoid bone. It is extraordinarily well protected. It is a small oval structure weighing about 0·6 gram in man. It is connected with the base of the brain by a stalk known as the infundibulum, continuous above with the tuber cinereum. It is grossly composed of three lobes, anterior, intermediary and posterior.

The anterior lobe is the largest. It develops embryologically by proliferation of the pharyngeal epithelium known as Rathke's pouch, which grows inwards to meet the posterior pituitary. The anterior lobe extends upwards and covers in part the anterior surface of the stalk, this portion being known as pars tuberalis. It contains very little connective tissue and is made almost entirely of columns of cells separated by capillary blood vessels. Three types of cell are distinguished, chromophobes, the smaller cells characterised by a poorly staining homogeneous cytoplasm, acidophiles that contain acidophile or eosinophile granules in their cytoplasm, and basophiles, containing basophile cytoplasmic granules. The chromophobes constitute 52 per cent. of the whole cell count, acidophiles 36·8 per cent., basophiles 10·9 per cent. (Rasmussen). There are, however, considerable individual variations. It is accepted by most authors that the chromophobe cell represents the antepituitary cell at rest, which when activated develops either acidophilic or basophilic granules. In pregnancy special cells develop, fairly large " pregnancy cells " of active secretion, without granulations but rich in mitochondria and staining well with eosin.

The intermediary lobe or pars intermedia derives from the posterior wall of Rathke's pouch. It lies in intimate contact with the posterior lobe, which it invests in its anterior surface. It is much smaller in man and other mammals. It contains basophile cells but without distinct granulation of their cytoplasm.

The posterior lobe or pars nervosa is derived from a downward growth of the floor of the third ventricle, to which it is attached by the pituitary stalk or infundibulum. It is composed of neuroglia cells, pituicytes and nerve fibres. The neuroglia cells resemble those present in other parts of the nervous system. The pituicytes, possibly modified neuroglia cells, contain brown pigment granules which have been compared with the lipochrome of the adreno-

cortical cells. Some hyaline or colloidal material (Herring's bodies) is found in this lobe but its significance is debated.

The pituitary, like all glands of internal secretion, is highly vascularised. Its veins have attracted much attention lately, and a hypophyseo-portal system has been described by Popa. The sinusoids of the anterior lobe are drained into special venules which ascend the stalk and break up into a capillary-network.

The Neuro-Hormonal Systems. The neuro-endocrine system can be divided into partial or secondary neuro-endocrine systems in the same manner as the other two sections of the nervous system are divided into secondary nervous tracts.

These neuro-hormonal systems follow two patterns of construction, the cerebro-pituitary and the direct cerebro-glandular.

The neuro-hormonal systems of cerebro-pituitary structure show three centres, cerebral, pituitary and glandular. The cerebral centre is mainly hypothalamic but works under cortical control. In a topographical sense there is no cortical centre, but only a general influence. The hypothalamic centre, however, may be a centre in the real topographical sense of the term, and consist, as Laruelle holds, of one special nucleus. The pituitary centre, mainly antepituitary, consists in cells secreting a particular endocrinotropin. A pressor impulse from the hypothalamic centre is transmitted to the antepituitary through the hypothalamo-antehypophyseal nervous tract already described, and stimulates secretion of an endocrinotropin, thyrotropin, for instance. The thyrotropin is transmitted by a humoral route to its glandular centre, the thyroid, and stimulates the thyroid cells to secretion of their specific hormone. These neuro-hormonal systems can function in their entirety, *i.e.*, beginning with the hypothalamic impulse (pressor or inhibitory), or may function from their pituitary centre, or may function solely through their terminal centre, the endocrine secreting hormone independently of any pituitary or hypothalamic stimulation. This last seems to be the usual mode of function normally. Nervous and chemical messengers activate the hypothalamic centre. Chemical messengers (the constitution of the blood flowing through the glands) stimulates pituitary and glandular effector centres.

The neuro-hormonal systems following the cerebro-glandular direct pattern do not use the antepituitary as a link. The impulse, pressor or inhibitory, passes directly through nervous routes from the hypothalamic centre to the particular endocrine. There are only two centres, cerebral (mainly hypothalamic) and glandular. Adherents to this pattern are the adrenal, insulin and hepatic systems, and those systems centred on the special metabolic hormones of the pituitary (growth hormone or phyone, diabetogenin, mammogenin, pituitary fat-metabolic hormone, antidiuretic hormone, vasopressin, oxytocin), because here the pituitary is not a link but a terminal glandular centre.

Both mechanisms may co-exist in a particular neuro-hormonal system, but one always preponderates.

CHAPTER III

GENERAL DESCRIPTION OF ENDOCRINE DISEASES

Constitutional Diseases. The internist interested in constitutional medicine considers the whole of the patient, departing from the system of constitutional regulation—genes, organisers, principally endocrine functions, psychological condition, neuro-vegetative system and nutrition. Some patients demand consideration nearly exclusively from this point of view, and are said to suffer from constitutional diseases. Diseases are artificial concepts but are necessary for the classification of knowledge. They are the working tools of the physicianand must be perfected as much as possible. The nosographical method provides the best way of classifying knowledge so that the individual patient can be approached.

Constitutional diseases are those diseases in which the morbid process involves particularly the system of constitutional regulation. According to the component of the system principally involved the following classifications can be adopted.

1. *Deep constitutional diseases.* Here the original disturbance is in the genes or organisers. An abnormal gene or gene complex has been transmitted by heredity or a normal gene has mutated. The mechanism of mutation is not clearly understood, but for practical purposes the action of parental, particularly maternal, metabolic disturbances due to various factors can be accepted. Genetic diseases are diseases of development. They can manifest themselves, however, late in life. Most diseases described as hereditary in the nosographies are genetic.

2. *Endocrine constitutional diseases.* These are the best known constitutional diseases. The mechanism of their production is similar to that of the preceding disturbances, *i.e.,* it consists in an interplay of the genogenic inferiority of a particular neuro-endocrine system with various environmental factors. These diseases form the subject of the present work; more details will subsequently be given.

3. *Psychogenic constitutional diseases.* The inclusion of psychiatry into the body of constitutional medicine and of internal medicine as a whole has followed from recent work, particularly from that done during the present war (it was the first world war that gave a powerful impetus to scientific psychiatry). As all groups of constitutional diseases are intimately connected it is imperative for the internist-constitutionalist, even if his favourite field is the endocrine or the nutritional diseases, to be thoroughly conversant with psychiatry, and for the psychiatrist to have mastered all the aspects of constitutional medicine.

4. *Nutritional constitutional diseases and avitaminoses.* These form another important group of constitutional diseases, interrelated with the other groups.

5. *Metabolic diseases and allergy.* The preceding groups of constitutional diseases have been isolated on the basis of the constitutional regulator predominantly involved. Some morbid conditions, however, have been

isolated on the basis of the metabolic disturbance which forms their physiopathology. All these classifications inevitably show much overlapping.

Allergic manifestations result from a constitutional disturbance and thus must be studied and treated within the frame of scientific constitutional medicine. The exclusive and superficial immunological point of view is to be avoided.

GENERAL DESCRIPTION AND THERAPY OF THE DISEASES OF THE ENDOCRINE GLANDS.

The conditions termed diseases of the endocrine glands are constitutional or metabolic diseases, *i.e.*, diseases due to rupture in the balance of the system of constitutional regulation and integration, with predominant involvement of one or more particular neuro-hormonal systems. They are diseases of metabolism, the metabolic disturbance being due predominantly to the faulty working of one or more neuro-hormonal systems.

The Two Forms of Endocrinism, Primary and Cerebro-pituitary. When a neuro-hormonal system is involved in its glandular centre, in other words, when an endocrine gland is primarily affected by the noxious factor, the result is a local, glandular or primary endocrinism. This may be hypersthenic, as when a glandular tumour secretes an excess of the particular glandular hormone, or hyposthenic, as when an endocrine gland is disturbed by an infective or toxic factor.

When a neuro-hormonal system is involved in its totality beginning at the diencephalic centre, the result is a cerebro-pituitary or cerebro-glandular endocrinism. A diencephalic impulse, either by direct stimulation or by a failure to inhibit, after transmission to the pituitary, causes that system to secrete an excess of a particular endocrinotropin. This endocrinotropin, when transmitted to the particular endocrine gland, brings about its hyperfunction. Other factors intervene and promote this total stimulating reaction of the diencephalon. These factors are probably connected with the special reactivity of the cells of the particular gland. Cerebro-pituitary hyposthenic endocrinisms arise by an analogous mechanism.

Primary pituitary endocrinisms determine secondarily other endocrinisms, because the pituitary centres of other endocrines are involved in the pituitary lesion. It is not necessary, however, to make of such endocrinisms a special category. They belong to the clinical and physiopathological picture of the primary pituitary endocrinisms.

Cellular Reactivity and Endocrinisms. The action of hormones depends on the reactivity of the cells on which they act. A hyperendocrinism depends not only on a hormonal hypersecretion but also on the hypersensitivity of the cells constituting the target of this hormone. In the same manner a hypo-endocrinism depends not only on hormonal hyposecretion but also on the diminished sensitivity of the cells to the particular hormone. Fuller Albright gives a striking illustration of the role of this reactivity by using the term Seabright syndrome. This expression derives from the fact that the male

Seabright bantam has female plumage, but the cause of this abnormality is not that the testis of the male bird produces female hormone but that the feathers of the male bird respond in an abnormal manner to the normal male hormone.

The reactivity of the cells depends on the genes and thus is of deep constitutional nature. It depends also, however, on the vegetative nervous system and on physical factors acting through this system. It is part of the general feature of " competence."

In an endocrinism there are thus two elements. There are endocrines in which th hormone plays the greater part, and these are more amenable to treatment. There are endocrinisms in which cellular reactivity plays the greater part, and these are more tenacious.

General Etiology of Endocrine Constitutional Diseases. The following etiological factors, often acting in combination (etiological constellation) determine the endocrinism.

A. Biological inferiority of the neuro-hormonal system. This may bear on the whole neuro-hormonal system or on the endocrine gland only. It is due to a defective gene for this particular neuro-hormonal system and is thus genogenic (I use this term in preference to genetic in order to avoid confusion between an endocrinism and a genetic disease). In many cases the biological inferiority is the predominant factor, and acts by a mechanism akin to the abiotrophic mechanism described by Gowers. Individuals are born with a biologically inferior or defective gland. The strain of life causes a rapid involution of this gland. In other cases individuals are born with a labile or defective neuro-hormonal system (considered in its entirety). The strain of life throws this particular system out of gear, causing either abnormal hyperfunction or rapid deficiency.

When this genogenic biological inferiority predominates we speak of biological inferiority or genogenic endocrinism. There is no reason for confusing this with genetic or deep constitutional diseases. In genetic diseases abnormal genes act directly on the cells and organs of the body and thus cause the metabolic disturbance. In genogenic disturbances an abnormal gene makes an inferior endocrine, and this in its turn causes its specific metabolic disturbance. There are of course mixed conditions, diseases in which an abnormal gene determines a constitutional metabolic disturbance by acting directly on the metabolism of cells and organs and by generating indirectly an abnormal endocrine.

B. Psychogenic factors. Psychogenic factors, sudden great nervous shocks or repeated nervous shocks (nervous tension) loom large in the etiology of endocrinisms. They can be explained by the direct action of a cerebrocortical disturbance on the diencephalic neuro-hormonal sections, but the more probable mechanism, as demonstrated experimentally by Selye, is that of an abnormal compensatory reaction of the whole neuro-hormonal system. This is hypersthenic at onset but may become hyposthenic through exhaustion. Selye's experiments demonstrate this mechanism for the adrenocortin and the thyrohormone systems. Thus a cerebro-pituitary endocrinism, hypersthenic or hyposthenic, originates.

C. Traumatic factors. A direct trauma on the endocrine gland or removal of this gland causes a primary endocrine deficiency. A trauma occurring far from the endocrine or a general trauma causes an abnormal compensatory reaction of a whole neuro-hormonal system and thus a traumatic cerebro-pituitary endocrinism. Again, Selye's experiments demonstrate this mechanism.

D. Infective factors. An infection localised on a particlar gland causes an endocrinism and thus a primary endocrine deficiency. An infection localised on the diencephalon (encephalitis) causes a cerebro-pituitary endocrinism by disturbing the diencephalic centre of a neuro-hormonal system. Such post-encephalitic endocrinisms are fairly frequent. The original encephalitis may not have been diagnosed. The virus infections of childhood —whooping-cough, measles—act through this mechanism and initiate endocrinisms. In most cases, however, infections act by determining an abnormal compensatory reaction of a particular neuro-endocrine system. This mechanism has been demonstrated by Selye for the adrenocortin system.

E. Toxic factors. These also may act directly on the endocrine, causing thus a primary endocrinism, or they may determine an abnormal compensatory reaction of an entire neuro-hormonal system, causing a cerebro-pituitary endocrinism.

F. Nutritive factors. Malnutrition, either general or referring to certain necessary food constituents (minerals, vitamins) may act directly by disturbing the metabolism and thus the function of a particular gland, the result being a primary endocrinism. The same factors may determine an abnormal compensatory reaction of a whole neuro-hormonal system, the result being a cerebro-pituitary endocrinism. As certain vitamins and minerals are necessary for normal function of a particular neuro-endocrine system, their absence may upset this neuro-hormonal system.

G. Neoplasms. These act through various mechanisms. Tumours arising in the endocrine glands may hypersecrete the hormone of the particular gland, and thus arises a neoplastic primary hypersthenic endocrinism. Tumours occurring in a particular gland may destroy it, and there arises a neoplastic primary hyposthenic endocrinism. Finally, tumours pressing on the diencephalon may upset the diencephalic centre of a neuro-hormonal system and thus give rise to a neoplastic cerebro-pituitary endocrinism which may be hypersthenic or hyposthenic.

All these etiological factors refer to the hormonal element of the endocrinism. Another series refers to the cellular target reactivity element. These are mainly genetic. Some individuals are born with genes which make for abnormal reactivity of these cells to a particular hormone. Disturbances of the neuro-vegetative system cause disturbance of the ionic equilibrium and thus of cell permeability, as do also certain exogenic factors, mainly physical, which act by upsetting the neuro-vegetative system.

All these etiological factors act usually in combination. The etiological constellation of each individual patient must be determined. There is in par-

ticular nearly always an interplay of factors of biological inferiority of a neuro-endocrine system with environmental factors and factors of genetic abnormal reactivity of the target cells. Endocrinisms arise from many "non-specific" factors.

General Symptomatology of Endocrine Diseases. For the sake of order in the complicated symptomatology of endocrine diseases I divide their symptoms into general, organ and biochemical, and group the symptoms belonging to any one of these categories into syndromes. In this I imitate the Greek empiricists, those fine descriptive clinicians, "syndrome" being a collection of symptoms referring to a particular function of organ.

The general syndromes refer to the form of the body (morphological syndrome), the mode of reaction to environment (reactivity syndrome), the state of sexual function (sexual syndrome), the mental condition (mental syndrome). These syndromes are essential in endocrinology.

The morphological syndrome or habitus is of great importance, as the endocrines contribute greatly to body form. The endocrinologist should be a a good morphologist, able to appreciate variations of form. The "artistic eye" is probably more important in endocrinology than in any other branch of medicine.

The reactivity syndrome refers to the reactivity of the patient to environment. It includes asthenia or activity, the mode of reaction to thermic stimuli, perspiration. It includes also reactivity to foods (likes and dislikes, hunger, thirst) and to toxic and infective factors. It thus includes allergic reactions. This syndrome, so much neglected in most modern textbooks, is fundamental in the understanding of the patient as a whole and in accurate and complete diagnosis of his neuro-endocrine, constitutional or metabolic condition.

The sexual syndrome is important because sexual functions depend on neuro-endocrine balance, and sexual disturbance indicates disturbance of this balance. The importance of sex in clinical medicine equals its importance in biology in general.

The mental syndrome could appropriately top the list. Endocrine and neuro-endocrine diseases disturb the "internal environment" of the cells. The cerebro-cortical cells are extremely delicate reagents to such changes, and thus their reactions indicate disease at onset. Further, the psychoassociational cortex or psyche by itself reacts intensely to the slightest disturbance of the system of constitutional regulation, wherever the first break has occurred. The modalities of the mental syndrome depend largely on the psychological state of the individual, his psychological structure. Over-compensation of the sense of inferiority engendered by the endocrinopathy is an important mechanism in the genesis of these symptoms.

The organ syndromes refer to all the organic systems of the body. They represent the disturbance of the various organs by the trouble generated in the biochemistry through the endocrinopathy.

The biochemical syndrome is elicited by laboratory investigations. It is acquiring an ever-increasing significance through advances in technique and

interpretation. It must be described in conjunction with the other symptoms because it is only within the frame of the other symptoms that it is of diagnostic value. The biochemical symptoms comprise the hormonic syndrome showing the hormones present in blood and urine. Certain special laboratory procedures such as the vaginal cytology investigation through the vaginal smear method developed brilliantly by Papanicolaou and his collaborators can be included in this section.

General Therapeutics of Endocrine-Constitutional Diseases. According to the contemporary view of endocrine diseases these are constitutional-endocrine diseases, *i.e.*, constitutional diseases with predominance of constitutional regulatory breakdown at the neuro-endocrine link. They therefore need treatment by constitutional methods including endocrinotherapy, but not by endocrinotherapy alone. One of the greatest mistakes has been to identify endocrinology with endocrinotherapy. Endocrinology is that branch of internal medicine dealing with endocrine-constitutional diseases. Endocrinotherapy is a therapeutic method used in these diseases but not the only method. It is possible that endocrinotherapy may be superseded in the course of time—recent work on the direct action of physical procedures on endocrine organs points to such a development—but endocrinology is enduring.

The basic constitutional procedure in treatment are the old Hippocratic methods, the general constitutional methods of psychotherapy, dietotherapy, physical medicine. The role of psychotherapy is immense, a fact easily understood from modern knowledge of the cortico-diencephalic connections and of the important psychological disturbances, of metabolic as well as psychological origin, met in neuro-endocrine diseases. No one can practise endocrinology without a deep knowledge of psychology and a natural skill in understanding and influencing the mental outlook of sick people. This is one of the many reasons which make endocrinology essentially the field of the clinician. The endocrinologist must even apply psychotherapy himself, for although some cases need a specialist psychotherapist, psychotherapy is in general more effective when it comes from the endocrinologist himself. Most endocrine patients object to a mere "word cure." They are very critical of the dogmatic procedures of psychoanalysis and its derivatives, and are influenced only by that psychotherapy which is practised, consciously or unconsciously, by a skilled clinician as an accompaniment to his more organic procedures and in the spirit of leadership which allows him to influence the mind of his patient.

Dietotherapy is also of great importance and merits careful study. An appropriate diet raises the tone of the body, the resistance of the patient against his infection or metabolic intoxication. The synergy which links certain food factors such as the vitamins to the endocrines is another argument for a careful dietotherapy in neuro-endocrine disease.

Physical medicine can be very effective in patients with endocrine disorders. Physical endocrinotherapy is a very powerful method, as I pointed out in my report to the British Medical Association Congress at Oxford in 1934. At the St. John Clinic I have continual opportunities of watching the good effects of phy-

sical procedures in endocrine disorders, which are often treated exclusively by these methods. Important work is proceeding in France on the initiative of Dausset, Huet and others, showing the direct influence on the endocrine glands of special physical procedures.

Endocrinotherapy, the utilisation of gland products, is undoubtedly a method of prime importance in contemporary medicine, but it is as highly specialised as neurosurgery, for instance, and thus is not for general practice. Too many mistakes have followed advertisements and medical propaganda directed to the general practitioner, and have been made possible by the facility with which hypodermic injections are given. In fact, the hypodermic syringe merits the words applied by Marshall Hall to the lancet, " a minute instrument of untold mischief." The schematisation of elementary textbooks does not correspond to reality, and therefore endocrinotherapy cannot be described in a book. Like a delicate surgical procedure, it does not lend itself to written description but depends on the capability, compounded of knowledge and principally of diagnostic power, of the " operating " internist. The usual procedure of endocrinotherapy is choice of a particular preparation in a particular dosage after a meticulous diagnosis not only of the disease but also of the person. The selected preparation is modified according to the tolerance and therapeutic reactions revealed by a careful following up. This diagnostic following up, which refers to the whole patient and to the patient as a whole, must be based on the totality of symptoms. The procedure brooks no short cuts, and laboratory tests are valuable only when judged according to the totality of symptoms. Often a slight change in the mental outlook, the way the patient enters the consulting room, his manner of talking, a flickering expression on the face, are far more valuable from the therapeutic point of view than the most elaborate laboratory investigations.

This technique of application of endocrinotherapy can be designated as the clinical-empirical method. It is opposed to the " rational " method based on laboratory investigation alone. The term " empirical " has acquired a bad connotation because it has been linked with the blind practices of unscientific healers. In fact, it derives from Hippocrates and the great Greek school of Empiricists, and constitutes the most accurate scientific method in clinical medicine, the true and particular method of clinical medicine. The term " rational " has a good connotation but gives only an illusion of precision. The rational method of yesterday is proved irrational to-day, and clinical observation has shown that " rational " procedures are usually unsuccessful. Let us not be the slaves of words. In the fourth century B.C. the son of Hippocrates himself, Thessalos, as well as Diocles of Karystos and Praxagoras of Kos, proclaimed the " rational " method in medicine as opposed to the clinical empirical method of Hippocrates. Their " rational " procedures have gone the way of those of their successors in the course of the ages, a way that shall be followed by the " rational " methods of many contemporaries. But the clinical empirical procedures of Hippocrates remain and will remain the basis of the healing art. Now that endocrinology has become

the nucleus of constitutional medicine, return must be made to the Hippocratic method.

Great results from endocrinotherapy have been demonstrated, and I believe that they would be even greater if we were better organised for its application. Endocrinotherapy presents two main difficulties—special knowledge and skill, and time. The treatments applied to maldeveloped children, for instance, may last for years. The fact that endocrinotherapy is a special method, as special as a delicate surgical operation, demands that the endocrinologist apply it himself, although as in surgical practice the general practitioner can give great assistance. The fact that endocrinotherapy may last a long time means expense and perseverance from the patient and relatives, and tenacity from the endocrinologist.

Endocrine preparations are not the only medicines used in endocrine diseases. Other constitutional medicines must sometimes be used if treatment is to be successful. Tonics, nervous sedatives, laxatives, may have important indications, as by raising the general tone they help to rid the patient of his disease. Medicines such as iodine, calcium and sulphur act more especially on the metabolic disturbances caused by the endocrinopathy. They are the metasyncritic medicines of the ancient Greeks, the alterants of the old pharmacopœias, the contemporary "modifiers of metabolism." To this group belong homœopathic preparations. Following Trousseau's principle, *La clinique prend son bien partout où elle le trouve,* and shunning all sectarian prejudice, I studied the homœopathic *materia medica,* and from the practice of the homœopaths I have adopted certain therapeutic methods which have proved very valuable to me. I do not hesitate to say that the complete endocrinologist should know the homœopathic *materia medica.*

Surgery is of great help in the treatment of early endocrine disorders, and the endocrinologist should be surgically minded although shunning the exaggerations of ultra-surgery. The surgical indications must be investigated, however, with great care.

Success in the surgical treatment of endocrine disorders depends on the collaboration of the endocrinologist. Independent action on the part of the surgeon is often detrimental to the patient. Just as the endocrinologist cannot himself operate on an exophthalmic goitre, a surgeon cannot deal with the constitutional endocrine side of the matter. Specialities have come to stay in medicine, but they are in reality specialities of points of view and not of sections of the body. A specialist is a physician who sees the whole patient from the particular point of view which he has selected. The endocrinologist sees the whole patient from one point of view, the surgeon or gynæcologist from another. An attempt to blend the two points of view in one physician is always to the detriment of the patient.

CHAPTER IV

NEURO-HORMONAL SYSTEMS CENTRED ON THE THYROID, PARATHYROIDS AND THYMUS

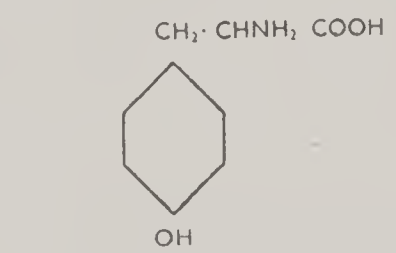
(THE BRANCHIAL GROUP OF ENDOCRINE GLANDS)

The neuro-hormonal systems centred in the thyroid, the parathyroids and the thymus can be considered in one group on account of embryological connections. All three originate in the branchial system. The thyroid arises from a median evagination of the endoderm between the first and second pharyngeal pouches, the parathyroids from the third and fourth pharyngeal pouches, the thymus from the third branchial pouch. This entails also topographical connections, these endocrines being situated in the neck and upper thoracic aperture.

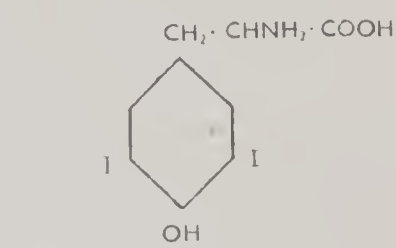
THE THYRO-HORMONE SYSTEM

The Thyro-Hormone. The thyro-hormone system is that part of the neuro-endocrine system which functions to produce thyro-hormone. Modern knowledge shows that thyroxin is only the nucleus of the complete thyroid hormone, not the complete thyroid hormone itself. For practical purposes, however, thyroxin and thyroid hormone or thyro-hormone can be considered synonymous. Chemical study of this hormone is principally derived from the work of Kendall, Harrington and Barger.

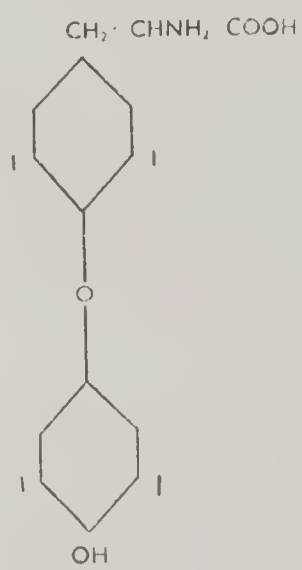
The thyroid cell absorbs iodine, ingested with food, from the blood. It combines it with tyrosin, an amino acid also coming from food (a necessary amino acid) and forms first diiodotyrosine and next thyroxin.



TYROSIN



DIIODOTYROSIN



THYROXIN

The thyroxin formed passes into the lumen of the acini, where it is stored in the colloid combined with thyroglobulin radicals. As demand arises, this thyroglobulin-thyroxin complex is passed back into the acinal cells and thence into the capillaries and the general circulation, where, according to Harrington's

hypothesis, it occurs in the form of thyroxin-radical-amino acid radical-diiodotyrosin. Normally the output in man is 1 milligram of thyroxin a day, the total circulating thyroxin being 10 mg.

The functions of thyro-hormone in life are the following:

1. Stimulation of oxidations. This is the basic function.

2. Stimulation of the catabolic phase of water metabolism. Thyro-hormone helps to detach water from the tissues and thus increases diuresis. In this respect thyroxin is antagonistic to the postpituitary anti-diuretic hormone (antidiuretin), which stimulates the anabolic phase of water metabolism. Œstrin and testosterone also have this particular antagonistic action.

3. Stimulation of the catabolic phase of protein metabolism. This results from the primary function of thyro-hormone stimulation of oxidations. In this respect thyro-hormone is antagonistic to the growth hormone of the ante-pituitary (phyone), to testosterone and in part to œstrin, which stimulate the anabolic phase of protein metabolism. Excess of thyro-hormone entails excessive loss of nitrogen, insufficiency retention of nitrogen. As for all proteins, thyro-hormone stimulates catabolism of creatine. In hyperthyroidism creatinuria occurs, and in hypothyroidean children urinary creatine is diminished.

4. Stimulation of glycogenolysis, thus contributing to the normal level of sugar in the blood. It is not known whether this is a direct action or is caused indirectly through stimulation of the adrenalin system. Excess of thyro-hormone may cause hyperglycæmia, hypothyroidism causing hypoglycæmia. On this point thyro-hormone is antagonistic to insulin, synergistic with adrenalin and diabetogenin.

5. Stimulation of the catabolic phase of fat metabolism. This also is secondary to the general stimulation of oxidations. Excess of thyro-hormone decreases the fat content of the tissues, particularly in the depots, and diminishes blood cholesterol. The contrary occurs in hypothyroidism. In this respect thyro-hormone possesses an action similar to that of a postpituitary fat-metabolic hormone (Raab's lipoitrin) and contrary to that of corticogenitalin, an adrenocortical hormone which stimulates the anabolic phase of fat metabolism, fat storage in particular.

6. Regulation of iodine metabolism. The thyroid takes iodine from the blood to form thyroxin, and stimulates detachment of iodine from the tissues. Excessive thyroid function involves excessive use of iodine, thus an excessive flow of iodine, with thyroxin, into the blood, excessive excretion of iodine in the urine, excessive detachment of iodine from the other tissues.

7. Stimulation of the excretion of calcium.

Those are the basic metabolic functions of the thyroid hormone. As all body functions depend on normal chemical processes, the thyroid contributes greatly to the normal working of growth, reactivity, sexual functions, nervous functions, circulatory functions and all other functions of the body. Hyper- or hypofunction of the thyroid disturbs these functions, with a mechanism and effects studied in the clinical description of the thyroid diseases.

Construction of the Thyroid System. The thyro-hormone system can be accepted as constructed on the direct cerebroglandular pattern, a direct nervous route uniting hypothalamus and thyroid gland. Sunder Plassmann holds that the nervous tracts joining hypothalamic to thyroid centre belong to the parasympathetic system, and has described terminal parasympathetic ganglionic cells in the thyroid. Nonides also has described the innervation of the thyroid. Such a direct cerebro-glandular route can function even if the nerves of the thyroid are regarded as purely vasomotor, because vasomotor influences react on the secretion of the gland. However, the structure of the thyro-hormone system is usually held to be cerebropituitary, and the usual cerebral, pituitary and glandular centres can be described.

The cerebral centre of the thyro-hormone system is hypothalamic but functions under cortical control. Its existence is demonstrated by many experimental and clinical facts. Hyperthyroidism arises from mental factors, or at all events is aggravated by such factors, and this indicates a cerebral centre of thyroid function. Strychnine, which stimulates central nervous functions, increases the activity of the thyroid (Indovina). Barbiturates, *i.e.*, hypothalamic sedatives, improve hyperthyroidean conditions (Fenz). Cold stimulates thyroid secretion. High altitude climates have a soothing action on hyperthyroidism. All these phenomena can arise only from a nervous centre. Falta and his school and also Uotila have done much work on this subject.

The pituitary centre is localised in the antepituitary cells secreting thyrotropin. Its existence is amply demonstrated. Hypophysectomy causes thyroid atrophy. A thyrotropic hormone, thyrotropin, has been isolated from the antepituitary (Loeb, Aron, 1929) and its thyroid-stimulating function well proved.

The glandular centre is the thyroid gland. This weighs about 30 gm. and consists of two lobes superimposed on the lateral surface of the larynx and connected by a small medial lobe, the isthmus. It occurs very early, in the third embryonic week, and arises as an entodermal pocket from the cranial end of the primitive intestinal cavity. It is thus in its origin an accessory gland of the the digestive tube. Its origin is found in humans on the surface of the tongue as foramen cæcum from which a duct emanates in some exceptional cases, the thyroglossal duct connecting the foramen cæcum and the thyroid and representing the upper part of the thyroid anlage. Usually this duct disappears except in the form of accessory thyroids in certain cases along its trajectory, and only the lower part of this digestive evagination constitutes the adult thyroid. Accessory or aberrant thyroids are frequent, and are encountered from the foramen cæcum to the aortic arch. Some are in the middle line and are connected with the thyroglossal duct. Others are lateral to the main gland and may even be encountered near or in the submaxillary glands. Most frequently they are under the main gland and may be intrathoracic. Thyroid tissue is found in certain ovarian teratomas.

Histologically the thyroid is composed of a stroma of connective tissue, vascular tissue and follicles or acini, which are its secretory units. The acini

are closed sacs, having lost all connection with other parts of the body. Their walls consist of continuous epithelium one cell deep, these cells, roughly cuboid, being the makers of thyroid hormone. Their lumen is the warehouse in which the product of this cellular activity is stored in the form of a substance, colloid, which is chemically a thyroglobulin. Thyroxin is part of the thyroglobulin molecule. The lumen is not completely filled by colloid but shows vacuoles, probably resulting from resorption of the colloid and thus indicating functional activity.

Like all endocrine glands, the thyroid is extremely vascular, its blood supply being estimated as 3–4 times that of the brain. Rich capillary plexuses exist around the acini to receive the internal secretions of the thyroid cells.

Nerves exist in abundance, originating from both the sympathetic and the parasympathetic systems. The sympathetic fibres arise mainly from the superior cervical ganglia, the parasympathetic from the vagus. These nerves enter into contact not only with the vessels but also with the follicular cells.

Mode of Function of the Thyro-hormone System. The thyroid system can function from any of its centres. It is probable that usually the thyroid gland functions primarily and independently, the antepituitary and cerebral centres exerting a function of control. The thyroid system can also function, however, through primary action of the antepituitary or the hypothalamus.

All these centres are activated by chemical messengers. A change in the constitution of the blood flowing through these centres stimulates or inhibits their function according to the needs of the body. The cerebral centre is activated also by nervous messengers coming either from the periphery through a reflex mechanism or from the cortex. Thus environmental factors, through the chemical manifestations they cause in the body and through their stimulation of the nervous system, regulate thyroid function.

The thyroid function is stimulated by meat, certain fats, foods low in iodine, vitamins C and E. The changes in the blood provoked by these nutritive factors can act directly on the thyroid gland; in fact, it has been demonstrated that thyroid hyperfunction following a diet low in iodine occurs in hypophysectomised animals. Vitamin A and copper inhibit thyroid secretion. Certain physical factors such as darkness and cold also stimulate thyroid function. They act through a nervous route on the hypothalamus. Light and heat inhibit thyroid secretion.

The basic law of the function of the neuro-metabolic system is harmony, balance. Whenever one component of this system is disturbed, balance is upset, because the other components endeavour to compensate the metabolic defects arising from the disturbance of that particular component.

The influence of any one neuro-hormonic system upon another follows two mechanisms, that of synergy-antagonism as regards certain metabolic regulation, and that of mutual stimulation-inhibition.

Synergy-antagonism bearing on certain metabolic regulation is apparent from study of the metabolic functions of thyroxin, and comparison with those

of other hormones.

There are few definite facts bearing on mutual stimulation-inhibition because, as in all systems of forces, the principle of relativity applies. The following considerations, however, arise. There is mutual inhibition between thymus and thyroid. Thymus administration aggravates hypothyroidsim. Theoretically it should improve hyperthyroidism, but this is not distinct. Adrenal cortex inhibits the thyroxin system, hence thyroid hyperfunction in certain cases of hypocortinism and improvement of hyperthyroidism by cortin. There is mutual inhibition of thyroid and gonads. Gonadal functions are inhibited in hyperthyroidism, and hyperthyroidism occurs frequently in hypogonadism. All these, however, are only certain clinical and experimental facts, and have no general application.

THE PARATHORMONE SYSTEM

The Hormone Parathormone. The parathormone system is that component of the neuro-endocrine system whose end-result is secretion of parathormone from its terminal or glandular centre, the parathyroids.

Parathormone has been isolated as the result of very painstaking work beginning with Moussu in 1898 and culminating in that of Hanson, Berman and Collip principally in 1925. It is a proteohormone containing 15·5 per cent. of nitrogen and traces of iron and sulphur. It contains either the NH_2 or NH group, mainly responsible for its activity.

Parathormone has the following metabolic functions.

1. Stimulation of the catabolic, mainly the excretory, phase, of phosphorus metabolism. Increased excretion of phosphorus occurs in hyperparathyroidism.

2. Stimulation of the catabolic phase of calcium metabolism. Calcium is detached in increased quantity from its reservoirs the bones, and passes into the blood and urine. Excessive function entails high calcilysis of the bones and a high calcium content of blood and urine. The contrary occurs in parathyroid hypofunction. This action on calcium metabolism depends on that of phosphorus metabolism. Calcium is detached from the bones to pass into the blood so as to re-establish the osmotic pressure diminished by the loss resulting from phosphorus excretion.

3. Normalisation of calcæmia, an important factor in homœostasis or constitution of the internal environment. A normal phosphorus excretion ensures normal passage of calcium into the blood. Parathyroid hyperfunction causes excessive excretion of phosphorus and thus hypophosphatæmia. More abundant calcium is detached from its reservoirs and penetrates into the blood to restore the osmotic balance. Thus hypercalcæmia occurs. The contrary happens when the parathyroids are in hypofunction.

The foregoing are the basic contribution of parathormone to the regulation of vital chemistry. The following also enter into consideration.

4. Stimulation of the catabolic phase of water metabolism. Parathormone is diuretic. Polyuria reaching diabetes insipidus may be observed in hyper-

parathyroidism, and parathormone injections have a very powerful diuretic action. In this respect parathormone is antagonistic to the water-retaining postpituitary and anti-diuretic hormone, to cortin and to insulin.

5. Stimulation of the anabolic phase of protein metabolism. Nitrogen retention occurs in hyperparathyroidism. In this respect parathormone acts similarly to the antepituitary growth hormone and testosterone, and contrary to cortin.

6. An action similar to that of insulin in carbohydrate metabolism. Parathormone injections diminish glycæmia, probably by increasing glycogen storage, diminishing glycogenolysis and diminishing peripheral glucose oxidation.

7. An action on other electrolytes, although nothing definite is known. It stimulates the catabolic phase of sodium and chloride metabolism (parathormone causes diuresis with chlorides). It appears also to stimulate the catabolic phase of magnesium metabolism, this ion being increased in the blood in hyperparathyroidism.

Homœostasis, the normal constitution of the internal environment, blood and humours, is necessary for the functions of life. In particular, a normal calcium content of the internal environment is necessary for maintenance of a balanced excitability of the nervous system. Parathyroid hypofunction and thus hypocalcæmia result in excessive neuromuscular irritability. This is the best known factor of parathyroid function but is not the sole factor. It is probable that normal calcium-phosphorus balance is necessary for other cellular functions, which are thus disturbed when this balance is altered by parathyroid hypofunction or hyperfunction.

Construction. This system also is constituted of a cerebral, a pituitary and a glandular centre. This conception is based mainly on the general biological principles of the structure of neuro-hormonal systems for there is no specific proof of a cerebro-pituitary structure such as has been demonstrated for the thyroxin system.

The cerebral centre (hypothalamic, functioning under cortical control) has not been clearly demonstrated. However, lesions of the parathyroid have followed lesions of the tuber cinereum.

The pituitary centre consists in antepituitary cells which secrete parathyrotropic hormone (parathyrotropin). The existence of such a centre also is debated, but certain facts indicate that the general cerebro-pituitary structure of the neuro-hormonal systems applies also to this particular system. Parathyroid tumours have been described associated with pituitary tumours (Handfield and Rogers, Chasnoff). Atrophy of the parathyroids follows hypophysectomy, although not constantly (Houssaye, San Martino, P. E. Smith). Hypoparathyroidism arises in the form of tetany in some cases of Simmond's disease. Antepituitary extracts cause hypercalcæmia, which can be prevented by parathyroidectomy (Anselmino and Hoffmann, Kemp and Marx, Hertz and Cranes). Injection of the urine of a patient with pituitary hyperplasia has caused hyperplasia of the parathyroids (Hertz and Albright).

The glandular centre is represented by the parathyroid glands. There are usually four, two on each side of the thyroid and attached to some extent to the posterior surface of the thyroid. The upper parathyroids lie amid the branches of the superior thyroid arteries, the lower near the inferior thyroid arteries, and may be embedded in the thyroid. There is, however, great variability in position and particularly in number, as accessory parathyroids are numerous and scattered over the cervical area and the mediastinum, above the thyroid, beneath it or embedded in the thymus. As many as twelve parathyroids have been found in one person, and parathyroid tissue has been discovered also in ovarian teratomas. The parathyroids are small glands, oval, lenticular or flattened, the size of a large pea but with great variations.

The parathyroids develop from the entoderm of the 3rd and 4th bronchial clefts in close proximity to the anlage of the thymus, and this explains why parathyroids are sometimes found embedded in the thymus. In humans they are differentiated about the 4th month of intrauterine life.

Histologically they are composed of a capsule of fibrous connective tissue with septa subdividing the substance of the gland. The glandular element consists in small acini, occassionally filled with colloid but differing from thyroid colloid by the absence of iodine. The glandular cells are of two kinds, water clear and oxyphile, probably representing different phases of cellular function. Water clear cells form the bulk of the glandular parenchyma, and are characterised by a faintly staining cytoplasm containing large amounts of glycogen and by a large and vesicular nucleus.

The usual vascularity characterising endocrine organ is found. The main blood supply comes from the inferior thyroid arteries, but there are so many anastomoses that circulation is maintained even after ligation of these arteries. Nerves are very scanty, and originate in the cervical sympathetic ganglia. They are the terminal effectors of a vasomotor mechanism.

Mode of Function. The parathormone system functions in general through its terminal glandular centre working independently and activated by chemical stimuli, mainly the changes in the calcium content of the blood flowing through the glands.

It may function from its pituitary or hypothalamic centre. Similar chemical stimuli activate or inhibit the parathyrotropin-secreting cells of the antepituitary, and the hyper- or hyposecretion of parathyrotropin through a humoral route influences the parathormone-secreting cells of the parathyroids. Similar chemical and also nervous stimuli influence the hypothalamic centre, which in its turn influences secretion of antepituitary parathyrotropin.

Stimulation of the cervical sympathetic in the cat produces hypercalcæmia (Speranska Spetanova). It is possible that this stimulus is transmitted to the antepituitary parathyrotropin-secreting cells, as the nervous connections between hypothalamus and antepituitary pass through the superior cervical sympathetic ganglia.

THE THYMUS SYSTEM

Construction. The thymus gland was known to the ancient Greek physi-

cians and its description is found in the writings of Ruphus of Ephesus (first century A.D.) and of Galen in the second century. It lies in the anterior part of the chest behind the manubrium sterni, in front of the trachea and above the pericardium. Its upper border may extend to the lower pole of the thyroid. It is composed of two lobes.

Its weight varies according to age. Hammar, who has done important work on the subject, gives it as 13·26 grams at birth, 37 grams between 11 and 15, 24 grams at 25, 19 grams at 35, 12 grams at 50, 6 grams at 70. There are many variations according to different authors, but all of them agree in showing the maximum weight between 11 and 15 years and subsequent involution.

It arises from the third branchial cleft, or sometimes the fourth. It thus has a common origin with the parathyroids, and for that reason parathyroid tissue is often contained within the thymus. The branchial origin gives rise to the epithelial-reticular elements of the thymus, but as this epithelial-reticular anlage is invaded by lymphatic formations the thymus becomes a mixed epithelial and lymphoid organ.

Each thymic lobe is composed of a number of lobules in which an outer portion or cortex and a central part or medulla are distinguished. The cortex is composed of small round cells, thymocytes, identical in appearance with lymphocytes, and thus resembles lymphoid tissue. Some reticular cells, however, also exist. The medulla also contains lymphocytes but the reticular cells are more prominent and form a definite reticular stroma. The characteristic formations of the medulla, however, are Hassal's corpuscles, which consist of a hyaline centre surrounded by layers of flattened cells with poorly staining nuclei. Reticular cells and Hassal's corpuscles are of epithelial ectodermal origin (Hammar).

The early development of the thymus, besides its derivation from an important endocrine formative region, resembles that of endocrine glands. An intricate network of epithelial cell cords and of blood capillaries and sinuses is formed, this being the characteristic histological feature of endocrine tissue. The thymus starts out to become an exocrine gland and at first there are indications of a duct. Later the thymus is ductless, although rudiments of its duct may still be seen.

The function of the thymus as a gland of internal secretion has been discussed by many, but their arguments against its endocrine nature I cannot find convincing. These authors base their view on the structure of the organ, which according to them is largely lymphoid. Structure, however, is never an important argument, especially as in the case of the thymus the reticular cells and Hassal's corpuscles are certainly not lymphoid and even the lymphoid origin of the thymocytes is open to discussion. Moreover, the lymphoid formations themselves cannot be denied an endocrine function, and in fact Carrell has isolated from them growth hormone substances, trephones. Another argument also is morphological, and is based on the size of the thymus, which has been declared to be too large for an endocrine organ. But

the liver, a most important metabolic endocrine organ, is even larger. The frequent failures to obtain thymus hormones and the discrepancies of thymectomies have the value of all negative arguments, particularly as they cannot be accepted as negative in all respects.

The great weight of evidence is in favour of the endocrine nature of the thymus. In the first place its peculiar change of size according to the phases of human development shows a distinct relationship with the metabolism of growth and of general development. Its origin from the third branchial cleft and its first development show an endocrine nature. It responds readily to spontaneous or experimental fluctuations in the endocrine system (Calcolari, de Re, Evans and Simpson, Hammar, Hart, Houssay, Marine and others), and thus seems to constitute a link in the endocrine chain. Clinically in particular it is seen hypertrophied in Graves' disease, acromegaly and certain hypogonadal conditions. Thymectomy improves conditions of myasthenia gravis.

We can even speak of a thymus system constructed on the same pattern as the other neuro-hormonal systems. A diencephalic centre has not been described, but a pituitary centre is evident from the increase of the thymus following the injection of certain antepituitary extracts.

Thymus Hormones. These have not been isolated. Carrell's trephones or growth factors are not specific, but are lymphocyte extracts obtainable as well from the spleen and lymph nodes. Glutathione, also possessing a growth-accelerating function, has been found in the thymus but as it exists in many tissues it cannot be considered as specific agent. Ascher and his co-workers have isolated a thymic principle which they call thymocrescin. Hanson has prepared a potent and stable extract with which the experiments of Rowntree, Clark and Hanson were made.

The thymus hormones seem to stimulate the fixation of calcium in bones and tissues and to increase phosphates in the blood. Thymectomy diminishes calcium in the bones (Bracci, Soli) and in the egg shell (Soli), and retards the repair of fractures (Glaessner and Has). When Hanson's thymic extract is injected in many generations of rats hypercalcæmia occurs from the second generation onwards (Rowntree and others). A similar action on phosphorus anabolism is probable but less clearly demonstrated. Hypophosphatæmia has been demonstrated in some experimental thymectomies (Nitresco and Benedetti, Martinetti). Hanson's thymic extract causes hyperphosphatæmia in rats from the second generation onwards. The many negative results preclude absolute acceptance of the foregoing facts, but hardened scepticism is never warranted on the basis of negative results.

Through these basic metabolic functions the thymus influences growth, mainly that of the bones. Thymectomy arrests the growth of animals in the experiments of Klose and Vogt, Mathieu Morel, Lucien and Parisot. Many results have been negative, however, and recently Segaloff and Nelson have failed to obtain any effect on growth through thymectomy perfomed on many generations of animals. Thymic extracts in injection accelerate growth. Experimentally this seems more definite, and has been obtained by Guder-

natsch, and principally by Ascher. In Rowntree's experiments the injection of Hanson's thymic extract in successive generations of rats causes definite acceleration in development and growth in the fourth and fifth generation, but the acceleration is only temporary, the rate of growth decreases after the second month and by the end of one year the experimental rats are as large as the controls.

The thymus seems also to regulate sexual development, but on this point experimental work is even more conflicting. Most facts, however, seem to point to an inhibition of this development. Thymectomy has provoked genital hyperplasia, when performed by some workers. Clinical conditions of hypogonadism are accompanied by thymus hyperplasia or at all events by arrested involution of the thymus. Injection of thymic extracts inhibit sexual maturity in the rat (Hewer). Experimentally many authors have obtained negative and even contrary results to those here quoted, but the clinical fact of defective thymus involution in human castration and hypogonadism in general remains unchallenged. Whether the experimental discrepancies can be explained by different functions of the cortex and medulla is at present a purely speculative hypothesis.

The thymus seems also to regulate immunity functions but here again both clinical and experimental findings do little to clarify the question.

In its basic metabolic function the thymus seems antagonistic to the parathormone system. It stimulates calcium fixation whereas parathormone inhibits it. By its action on growth and development the thymus seems to be synergistic with the phyone system and antagonistic to the pineal and parathyroid. (It should be remembered that an anti-growth factor has been described in the parathyroids.) By its action on sexual development the thymus seems antagonistic to the testosterone and œstrin systems and synergistic with the pineal. In its immunity-regulating function the thymus seems to work synergistically with the adrenal cortex. Zondek accepts also a general antagonism between thymus and thyroid. All metabolic functions and thus all functions of the body in general are under the influence of a stimulating-inhibiting system of forces. The thymus has its place in this system, which explains the changes detected in that organ when other elements of the system of constitutional regulation are disturbed. Hence the thymic hypertrophy of Graves' disease and myxœdema (for different reasons), and the arrested involution of the thymus in hypogonadism, acromegaly, Addison's disease, post-hypophysectomy and post-adrenalectomy states.

CHAPTER V

NEURO-HORMONAL SYSTEMS CENTRED ON GONADS AND ADRENALS

(THE LOWER ABDOMINAL GROUP OF ENDOCRINE GLANDS)

Gonads and adrenal cortex can be described in a special group on account of embryological and topographical connections. They are abdominal glands.

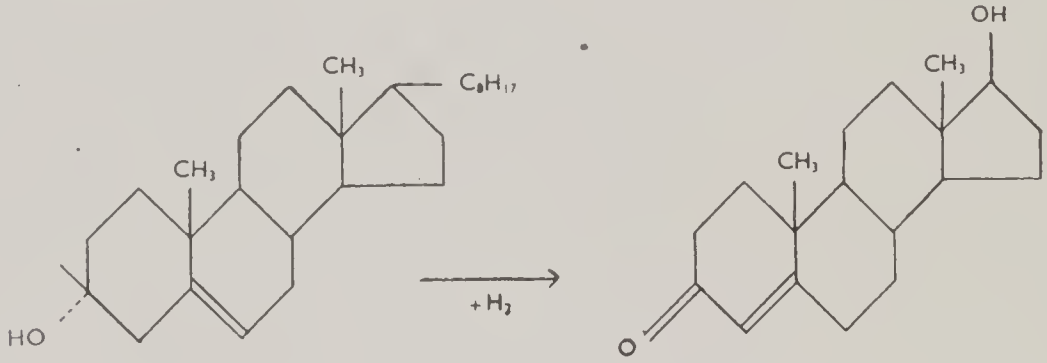
and both arise from the urogenital ridge. The adrenal medulla arises from cells of the outer germ layer which are also the anlage of the autonomic nervous system, but becomes intimately connected with the adrenal cortex.

THE TESTOSTERONE SYSTEM

The testosterone system is that component of the neuro-endocrine system which functions to secrete testosterone from its terminal or glandular centre, the interstitial gland of the testis.

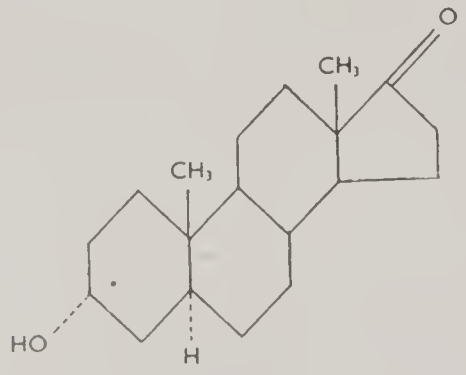
The Hormone and its Functions. Testosterone, known also as the male hormone, has been isolated by a series of researches starting with the crude extracts of Brown-Sequard in the eighties, progressing with the lipoid extracts of Iscovesco in 1912, and culminating in the more purified extracts of the American workers F. Koch, L. C. McGee, C. R. Moore, M. J. Gallagher from 1922 onwards and the chemical determination obtained by Butenandt and the Ruzicka group in Basle. Testosterone is accepted as the typical and exclusive testicular androgen.

It is produced by the interstitial cells of the testis, probably from cholesterol or similar metabolic products and is, like cholesterol, a sterol.



CHOLESTEROL TESTOSTERONE

It is excreted in the urine as androsterone.



ANDROSTERONE

Testosterone regulates certain general chemical or metabolic processes of the body, but acts principally on the cellular metabolism of the extra-gonadal (the so-called secondary and tertiary) sexual features, to which it gives the male aspect and which it helps to develop.

As regards the general metabolic functions it causes :

1. Stimulation of the anabolic phase of protein metabolism. Injections of testosterone cause nitrogen retention. In this respect testosterone acts similarly to antepituitary growth hormone and contrary to cortin and thyroxin. It stimulates also the anabolic phase of creatine metabolism. In prepuberal castrates the prepuberal creatinuria continues throughout life and is corrected by testosterone injections.

2. Stimulation of the anabolic phase of water metabolism. It is a water retainer like postpituitary antidiuretin and cortin, and thus acts in opposition to thyroxin and parathormone.

3. Stimulation of the anabolic phase of sodium and chloride metabolism. Testosterone injections cause retention of these elements. Here also the action is similar to cortin and contrary to thyroxin.

4. Stimulation of the anabolic phase of potassium metabolism, acting in the contrary sense to cortin. Testosterone causes potassium retention.

5. Stimulation of the anabolic phase of inorganic phosphorus and sulphate metabolism.

Altogether testosterone shows a distinct somatotropic action. Either on the basis of these biochemical functions or else through direct vascular action testosterone is a vasodilator, and thus in opposition to adrenalin and vasopressin. It does not seem to exert physiologically a direct action on the rate of oxidations. It is true that in castrates and eunuchoids basal metabolism is diminished, but this is because the thyroxin system is depressed through the hypotestosteronism, testosterone normally stimulating the thyroxin system.

As regards special action on the cellular metabolism of the sexual tissues, the following are the essential features.

1. Testosterone probably influences the vitality of the spermatic cells.

2. It stimulates development and maintenance of function of the external genitals (penis, scrotum) and the genital tract (vas deferens, seminal vesicles, prostate).

3. It stimulates closure of the epiphyses. In hypotestosteronism the epiphyses remain open a long time, in hypertestosteronism they close very early.

4. It stimulates muscular development. In hypotestosteronism the muscles are undeveloped, but over-developed in hypertestosteronism.

5. It stimulates hair to develop according to the male type of distribution, and thus promotes hair on the body and face and inhibits the development of hair on the scalp.

6. It stimulates the sebaceous glands of the skin. In hypertestosteronism seborrhœa and acne occur.

7. It probably directs fat distribution in the male.

8. It stimulates potency, acting in this respect synergistically with the nervous regulators of this function and in general. It exerts a general masculinising influence and erotises the cerebral cortex at puberty towards the male type of libido.

Construction of the Testosterone System. The testosterone system is constructed on the cerebro-pituitary pattern. There is no demonstration of

any direct cerebro-interstitial testicular gland structure, although recently Harold Okkels has described nervous terminations in contact with the interstitial cells.

The usual three centres are described, cerebral, pituitary and glandular.

The cerebral centre (hypothalamic function under cortical control) is well proved. Cerebral cortical action on the sexual functions in general is clearly demonstrated, and some authors, Economos for instance, describe a cortical sexual centre which they place in the insula. Special influence on the secretion of β-gonadotropin and testosterone, however, can only be surmised. The diencephalic or hypothalamic centre of the testosterone system is more clearly demonstrated, although here also analogy is necessary with the general lines of testicular function. Many experiments show that olfactive and visual stimuli promote development of the gonads and of the mating instinct. These stimuli can act only through nervous routes *via* the hypothalamus. Natural light causes the testes of ducks to develop, darkness causes them to atrophy (Benoit). Ferrets subjected to light mate at unusual periods (Bissonette). The reproductional state of fish is controlled by changes of temperature (Craig Bennett). These are only a few of the many experiments on the subject.

The pituitary centre is represented by the antepituitary cells which secrete a special gonadotropic hormone for the interstitial gland, luteostimulin or L.S.H. but preferably termed beta-gonadotropin, as L.S.H. refers to the female function. The existence of this centre has been amply demonstrated and beta-gonadotropin isolated with a considerable degree of purity. It is a proteohormone with the principal function of stimulating the testicular interstitial cells to production of testosterone. It has, however, some independent functions. It stimulates descent of the testicles during development and also promotes development of the interstitial gland itself, hence the frequently used term gonadotrophin. It is similar to a hormone produced by the chorion in pregnancy, called chorionic gonadotropin. It is similar in males and females.

The glandular centre of the testosterone system is represented by the interstitial cells of the testis, which although scattered can be considered as constituting one gland, the interstitial gland of the testis (Ancel and Bouin). These cells, first described by Leydig in 1850, are believed by many authors to develop from the cords, described by Pflüger, which give rise to the seminal tubules, but others regard them as modified connective tissue cells. They appear in the 45 mm. human embryo and are very numerous by the fifth month of fœtal life. They disappear almost totally after birth but reappear at puberty. They reach their highest number in the 10th–19th years, and then gradually diminish.

They are situated between the connective tissue sheaths supporting the seminiferous tubules. Shattock pointed out their histological resemblance to the cells of the adrenal cortex. They are flattened, polyhedral, yellow in colour, and contain lipoid globules in their protoplasm. They constitute 13 per cent. of the whole testis. There is an ample network of capillary blood

vessels among these cells, the arrangement being that seen in all glands of internal secretion.

Mode of Function of the System. The testosterone system can function from any of its centres. Usually, however, it functions from its antepituitary and hypothalamic centres. Its function starts at puberty, although rudimentary function may have occurred earlier.

The hypothalamic centre gives the first impulse towards puberty, for reasons as yet obscure. The only known fact is that certain environmental factors activate this centre, such as light in the case of certain animals, and probably sexual excitation in man. There may also be a question of biological rhythm inherent in the cells of this centre. The hypothalamic impulse transmitted to the antepituitary beta-gonadotropin cells causes secretion of this hormone, which when transmitted by a humoral route to the interstitial gland stimulates the cells of this gland to secrete testosterone.

From that moment testosterone secretion is regulated by a delicate system of hormonal balance. When the secreted testosterone has reached a certain level in the blood it depresses the antepituitary gonadotropin-secreting cells either directly or through their hypothalamic centre. The cessation of beta-gonadotropin secretion, however, causes a fall in testosterone secretion and thus releases the brake on the beta-gonadotropin-secreting cells, which begin once more to secrete their interstitial-cell-stimulating hormone, and so on. Thus testosterone secretion is a self-regulating mechanism.

It is possible also that testosterone function begins primarily at the pituitary centre, activated by various chemical factors.

Normal testosterone function requires perfect balance of all elements of constitutional or metabolic regulators. Thus, testosterone secretion may be disturbed by deficiencies in the nutritive regulators. In particular, vitamins E, C and B seem necessary. Balanced function of the other neuro-hormonal systems also is necessary. Thus testosterone secretion may be disturbed in thyroid, adrenal and insulin deficiencies. There is in particular a special antagonism between the testosterone and growth hormone (phyone) systems.

Secretion of testosterone begins in humans in the 10th–13th years, and is first of low grade. From puberty onwards there is full secretion. Decline starts between 60 and 70, but there is evidence of good production in later years. In humans the secretion is continuous, but in certain animals it occurs only at certain periods coinciding with the natural breeding periods, times of rut.

In the urine the testosterone excretory product, androsterone, which is a 17-ketosteroid, is determined with the other 17-ketosteroids representing the excretory products of the adrenal cortex. In children under six, 0·1 mg. of androsterone plus adrenocortical 17-ketosteroids is found in the urine for 24 hours, in adult man, 7–27 mg.

The Testosterone System in the Female. Woman also secretes testosterone with other androgens. This secretion comes from the adrenal cortex but may also originate in certain cells of the hilum of the ovary, male

remnants of the bisexual gonad of the embryo. The role played by these androgens in the normal physiology of the female is obscure, but must be important, as the quantity of 17-ketosteroids in the urine of women is nearly as great as that in men. It should not be forgotten that the action of a hormone depends in great part on the reactivity of the cells on which it acts, and we can thus hold that the reactivity of female tissues is such that testosterone makes for their development. In fact, experimental work has shown that in a certain small dosage testosterone stimulates the growth of ovaries, uterus, tubes, and causes premature opening of the vagina and œstrus in castrated female rats, and has an œstrogenic action on the sexual skin of the female monkey and induces ovulation in Xenopus levis. In human females it causes heightened susceptibility to psychic and somatic sexual stimulation and greater intensity of sexual gratification and is a real aphrodisiac in strong doses (Greenblatt).

Thus testosterone may have an œstrin effect on the female. In some cases it has a progestin effect, maintains pregnancy in castrated rats during pregnancy and causes hypertrophy of corpora lutea.

The deeper the study of endocrinology the more apparent it becomes that there is a basic integration of the body-mind and that the action of all stimuli depends on the pattern laid down by this integration. Testosterone is a " male hormone " only in the male.

The Male Gametogenin (Inhibin) System

Knowledge of such a neuro-hormonic system corresponding to the œstrin system of the female is very scanty. A cerebral centre can be surmised. The pituitary centre is well demonstrated, and consists in basophile cells secreting *a*-gonadotropin or folliculostimulin (F.S.H.). In the female *a*-gonadotropin stimulates the follicular cells to production of œstrin. In the male does it stimulate the spermatic cells to produce a similar hormone? At all events, *a*-gonadotropin seems to exert a stimulating action on spermatogenesis. A testicular gametogenin (corresponding to œstrin) is accepted as inhibiting the action of testosterone on the development of the prostate. Its failure is accepted as a factor of prostatic hypertrophy.

The Œstrin System.

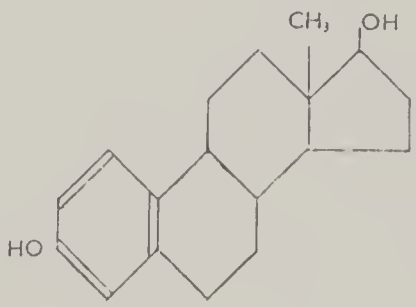
The Hormone Œstrin. The œstrin system is that part of the neuro-metabolic system reserved for secretion of œstrin, a hormone secreted ultimately by the ovarian follicle, probably by the theca cells of this formation. The hormone has been isolated after a series of painstaking researches.

In 1893, Regis treated with crude ovarian extracts a case of menopausal psychosis. In 1895, Curatullo and Tarucci published their work on the internal secretion of the ovary. In 1900, Emil Knaus and Josef Halban, both of Vienna, carried out important researches on the internal secretions of the ovary. In 1912, Henri Iscovesco, working at Dastre's laboratory in Paris, made the first good extract of a potent preparation from the ovary, using lipoid solvents such as alcohol, ether and acetone. It was only in 1923, however, that thanks

to the introduction of the vaginal smear test by Stockard and Papanicolaou, a more accurate technique of research became possible and Allen and Doisy obtained an active principle from the ovarian follicles. In 1935, McCorquodale, Thayer and Doisy found the chemical formula of this active principle, known since as œstradiol. This chemical determination was based on research into the excretion products of the follicular hormone in the urine (found by Loewe in 1926, Aschheim and Zondek in 1927, obtained in crystalline form by Allen in 1929, and determined chemically by Butenandt in 1936).

It is possible that œstrin occurs in the body in a form other than œstradiol, but up to now only œstradiol has been clearly found.

Thus œstrin, or more accurately œstradiol, has been shown with the following formula.

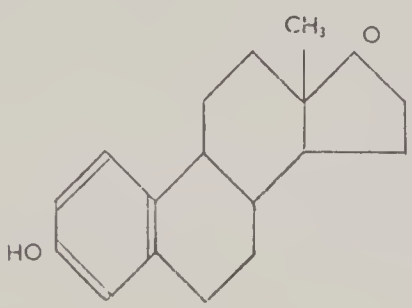


ŒSTRADIOL

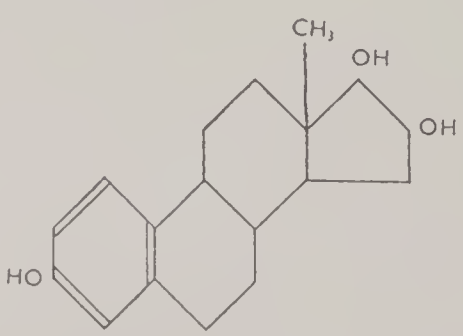
It is a sterol and a derivative of the phenanthrene nucleus.

After being secreted by theca cells œstradiol passes into the blood, where it can be detected. After performing its function it is partially inactivated by the liver and partially excreted in the urine in the form of special excretory products, œstrone and œstriol.

Œstrone (known also as ketohydroxyœstrin or theelin).



ŒSTRONE (THEELIN)



ŒSTRIOL (THEELOL)

Œstrin (*œstradiol*) plays an important role in the physiology of the body-mind. It acts as regulator of certain general metabolic functions and of the cellular metabolism of the extra-gonadal sexual characters. The two are probably connected.

On general metabolic functions the following action has been accepted.

1. Stimulation of the anabolic phase of protein metabolism. Experimentally œstrin, like testosterone, in strong doses causes retention of nitrogen. The stimulation of creatine anabolism is important. In ovariectomy (œstrin deficiency) creatinuria and creatininuria occur.

2. Regulation of fat distribution on the female pattern.

3. Stimulation of the anabolic phase of water and sodium metabolism. Thus excessive œstrin causes retention of water and sodium chloride.

4. Regulation of the pigmentation metabolism, bearing mainly on skin pigment. This is related to the seasonal changes of pigmentation correlated to the sexual activities of certain animals. The pigmentation of pregnancy in humans is probably due to œstrin excess.

5. Stimulation of epiphyseal closure. Thus in œstrin hyperfunction the epiphyses close early with a resultant small stature, the contrary occurring in hypo-œstrinism.

The cellular metabolism of the sexual organs undergoes the following influences of œstrin.

1. Stimulation of the growth of the female genital tract (uterus, tubes, vagina). The precise mechanism of this stimulation is not known but improvement of circulation is a distinct factor. Œstrin acts as a vasodilator, and the blood flow through these organs is increased. There is also, however, a direct action on the cells.

2. Stimulation of the development of the breasts, in which function œstrin acts in combination with progesterone and prolactin. Œstrin stimulates the development of the ducts. Progesterone and prolactin, acting during pregnancy, develop the acini, the actual milk-producing terminations of the ducts.

3. Promotion of the morphological feminine features. It contributes to the special hair and fat distribution of the female. Finally, it seems to act on the cerebral cortex so as to " erotise " it, *i.e.,* to promote feminine libido and sexual emotion.

4. All these functions of œstrin are performed at puberty. Later, when the genital organs and female features have reached full development, œstrin maintains their normal metabolism and thus their normal form and functions. It contributes to the sexual or menstrual cycle, the first half of this cycle, characterised by endometrial proliferation, being under œstrin influence. In animals the œstrin phase of the cycle is the phase of œstrus or heat during which the female desires and is ready to receive the male. Although in humans œstrus does not occur because the female is ready to receive the male at any time, psychological studies have shown an increase of libido during the œstrin phase (Benedek and Rubenstein).

Construction of the System. *The Cerebral Centre.* This centre is hypothalamic and functions under cortical control. In it originates the initial pressor or depressor impulse of total œstrin function. This impulse is transmitted through hypophyseo-hypothalamic connections to the antepituitary centre of the œstrin system (the antepituitary cells secreting *a*-gonadotropin) and *a*-gonadotropin secretion is accordingly stimulated or depressed. *a*-gonadotropin (or F.S.H.) is transmitted by humoral routes to the glandular centre of the œstrin system, the ovarian follicles, and promotes secretion of œstrin by these cells.

The existence of this centre is clearly demonstrated by a series of experi-

ments and clinical observations indicating the cerebral influence on gonadal functions. Thus lesions of the hypothalamus, with integrity of the pituitary, cause atrophy of the gonads (Camus and Roussy, Cahan). Section of the pituitary stalk causes genital atrophy in cats (Harris). In general, certain sex processes such as ovulation, menstruation and associated histological changes of the vaginal epithelium (Stockard and Papanicolaou) which occur rhythmically are easily disturbed by psychic factors such as fear, mental strain and other emotional states. The regularity of menses in normal women points to a central regulating factor (Theobald). Sexual excitement leads to ovulation in rabbits (Brambell and Parkes). Electrical current applied to the head or spinal cord of the rabbit causes ovulation (Marshall and Verney). Stimulation of the hypothalamus elicits ovulation (Harris, Haterius), and Westman and Jacobson proved that such a hypothalamic stimulation failed to produce ovulation after transection of the stalk, whereas it regularly did so when the nerve fibres connecting hypothalamus and pituitary are intact. Whereas rabbits ovulate when copulation takes place (sexual excitement) this does not occur if the stalk is cut even a short time before copulation. It is unnecessary to cite all the experiments on the subject. Hypothalamic influence on the gonadotropic secretion of the antepituitary and thus on the ovarian hormones has been amply demonstrated. Some experiments point to a special hypothalamic action on œstrin secretion. Thus increased illumination produces œstrus in the female rabbit.

The pituitary centre. This is composed of the basophile cells of the antepituitary which secrete a hormone (*a*-gonadotropin or folliculostimulin) stimulating the cells of the Graafian follicles to secrete œstrin. Its existence is amply proved by the effects of hypophysectomy on the ovaries, and principally by the isolation of *a*-gonadotropin, a proteohormone, and demonstration of the follicle-stimulating properties of this hormone. Most expermental work was conducted on antepituitary gonadotropin, which is a mixture of *a*- and *β*-gonadotropin, but recently Fevold, Hisaw and Leonard isolated with some degree of purity *a*-gonadotropin from this mixture of hormones.

The glandular centre, the ovarian follicle. The Graafian follicles which constitute the terminal or glandular centre of the ovarian follicle are round egg chambers embedded in the ovarian stroma. They are lined with cells forming a layer appearing granular under low magnification and hence called granulosa cells. Just outside the granulosa layer is a fine layer of cells called theca interna, which are well supplied with blood vessels and are probably the source of œstrin. A group of granulosa cells, the cumulus oophorus, juts out into the lumen of the follicle and encloses the ovum. The human ovary contains many Graafian cells. Haggstrom has counted 420,000 in a 22-year-old woman. They are all present at birth, no follicle developing during life thereafter. Of this enormous number of follicles only about 400 mature and expel their ova. The others become atretic, but although unimportant for ovulation, they secrete œstrin. The developing Graafian follicle becomes transformed, after expelling its ovum, into the corpus luteum, whose cells, according to

some authors, also secrete progestin as well as œstrin.

Mode of Function of the Œstrin System. This system can function from any of its centres. It functions very little before puberty but at that stage of life a diencephalic impulse, probably bound up with a special biological rhythm, stimulates antepituitary secretion of *a*-gonadotropin which, in its turn, stimulates the ovarian follicles to secrete œstrin. From that moment œstrin secretion is regulated in the same manner as testosterone secretion in the male, by a self-regulating mechanism. Increased œstrin in the blood depresses antepituitary *a*-gonadotropin secretion, directly or *via* the hypothalamus. The *a*-gonadotropin depression brings about a fall in œstrin secretion, the latter hormone diminishes in the blood, and thus the *a*-gonadotropic cells, free of the œstrin brake, begin to secrete once more and thus stimulate œstrin secretion again, and so on.

At the climacteric œstrin function begins to wane irregularly, and that phase of life exhibits a hormonal storm. Phases of true hyperœstrinism (hypersecretion of *a*-gonadotropin and œstrin) occur, as well as phases of dis sociated secretion, *a*-gonadotropin being secreted in great quantity but œstrin secretion being low.

During pregnancy the placenta takes over the functions of œstrin secretion.

The secretion of œstrin is cyclical. It shows two peaks corresponding to ovulation (roughly the 8th–12th days of the cycle) and to the immediately premenstrual phase.

Once secreted, œstrin passes into the blood, is partly inactivated in the liver and then passes into the urine in the form of its metabolites, œstradiol and œstrone.

An adult non-pregnant woman excretes an average of 300 γ of œstrin (in terms of œstradiol) per diem in her urine, with great variations. All this, however, does not come from ovarian œstradiol. Some comes from the œstrogenic substances secreted by the adrenal cortex and some from food, œstrogenic substances occurring in animal products and plants such as yeast and potatoes.

The function of the œstrin system as of all other neuro-endocrine systems follows the law shown by the function of the genes. It is part of a system of forces, and thus the other components of the system should be in perfect harmony. Equilibrated function of the other neuro-hormonal systems, of the vegetative nervous system and of the environmental, principally nutritive, factors is necessary. Disturbance in the œstrin system upsets the balance of the other components of the system of constitutional or metabolic regulation, and *vice versa*. It is unnecessary, however, to dwell on experiments showing the various synergists and antagonists because these can have only a limited application. Whether an œstrin disturbance causes hyper- or hypofunction of another neuro-hormonal system depends on the special condition of the system of forces forming the constitutional regulatory system at that particular moment.

Œstrin in the Male. Œstrin exists in the male. Œstrogens appear in male urine nearly as abundantly as in the female, although the androgens/

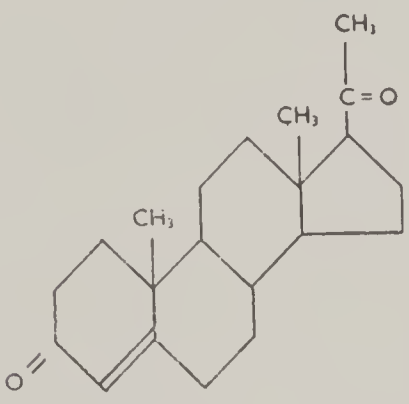
œstrogens ratio differs, androgens preponderating in the male.

These œstrogens do not correspond to ovarian œstradiol. Most of them come from the adrenal cortex, but lack of absolute chemical determinations leaves the question obscure. It is held by Zondek that testosterone, the typical male hormone, can be metabolised into œstrogens.

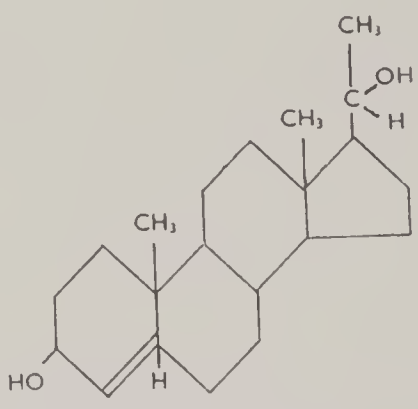
It is not known whether this œstrin plays a role in the normal physiology of the male. In morbid conditions of testosterone failure in the male, the male œstrin acts unchecked and causes feminisation.

The Progestin System.

The Hormone Progestin. The progestin system is that part of the neuro-metabolic system of which the terminal effect is secretion of progestin by the cells of the corpus luteum. Progestin has been isolated in increasingly pure form by workers in the United States, mainly by George W. Corner, Willard M. Allen, Hisaw and his co-workers. Its chemical formula was determined by Slotta, Ruchsig and Fels, and Butenandt succeeded in synthesising it from cholesterol. It is probable that the lutein cells produce progestin from cholesterol.



PROGESTERONE



PREGNANEDIOL

Its task done, progesterone is converted into pregnanediol (Ethel H. Venning, J. S. V. Browne, 1936), a substance inert from the endocrinological point of view (addition of 6 atoms of H). The body rids itself of this substance by attaching it to a substance available from the starches and sugars of food, glycuronic acid. To this an atom of sodium is added, and the ultimate product, sodium pregnanediol glycuronate, passes into the urine.

The principal action of progesterone is on the endometrium, which progesterone directs to pass from the proliferative to the secretory phase. In pregnancy, progesterone carries this action further into the development of the placenta, and in the very early days of pregnancy stimulates the endometrial cells to produce substances for the nutrition of the embryo.

Progesterone inhibits and soothes uterine motility. Through this action the spontaneous rhythmical contractions of the uterine musculature caused by œstrin cease. This is important in pregnancy, as the quietened uterus allows the embryo to be safely implanted.

Finally comes an influence on breast development, also in relation to pregnancy. Œstrin has already stimulated the development of the ducts. Progestin develops the acini. Later prolactin-mammogenin initiates lactation from the acini.

Construction and Mode of Function of the Progestin System.

The usual cerebral, pituitary and glandular centres can be described.

The cerebral centre is cortico-hypothalamic, mainly hypothalamic. Its existence is demonstrated by the considerations applying to the cerebral centre of the œstrin system, all these experiments and clinical observations showing central nervous influence on the gonads. Experimental pseudo-pregnancy, *i.e.*, the production of ovulation and a progestational endometrium in the rabbit through introduction of a rod into the vagina is definite proof of the role of this centre.

The pituitary centre consists in those antepituitary basophile cells which secrete β-gonadotropin or luteostimulin. Its existence is demonstrated by experiments with hypophysectomy and by isolation of β-gonadotropin and experimental proof of the corpus luteum stimulating action of this hormone.

The glandular centre of the progestin system is the ovarian corpus luteum which succeeds the mature Graafian follicle after the ovum has been expelled. After the rupture of the follicle the granulosa cells, which had already begun to swell, fill with yellowish double refractive particles of lipoidal character and resemble the cells of the adrenal gland. They become the lutein cells. Immediately after rupture hæmorrhage occurs into the follicular cavity. The walls collapse and the folds thus formed make the boundaries of the corpus luteum. A rich network of capillaries, as in all glands of internal secretion, surrounds the corpus luteum and penetrates it, coming into contact with the lutein cells. The human corpus luteum is a mass $\frac{3}{4}''$ in diameter. It was described first by Regnier de Graaf on 1672, but it was only in 1898 that Auguste Prenant of Nancy pointed out its internal secretory nature. Ludwig Fraenkel, in 1903, and Ancel and Bouin, in 1910, showed that it plays a role in the protection of the embryo.

When pregnancy does not occur the corpus luteum disintegrates after roughly two weeks of life. The lutein cells are completely absorbed, while the connective tissue fibres swell and form the corpus albicans, the end result of the follicle and corpus luteum. The corpus albicans itself disappears in five years. When pregnancy occurs the corpus luteum persists, develops, and progesterone is secreted during the whole period of pregnancy, after which the corpus luteum regresses.

Nervous and chemical stimuli acting on the hypothalamic centre, or chemical messengers acting on the pituitary centre, stimulate transformation of the follicle into corpus luteum. The most important chemical messenger is probably œstrin.

Similar nervous and chemical stimuli acting on the hypothalamus initiate total function of the progesterone system. Chemical stimuli acting on the pituitary also cause progesterone secretion. The cycle of secretion is similar to

that of œstrin. When the progesterone level becomes high β-gonadotropin secretion ceases, the progesterone level falls, and β-gonadotropin begins once more to be secreted. Here again the mechanism is self-regulating. An independent secretion from the corpus luteum itself is also possible. During pregnancy, nervous and chemical messengers come from the embryo.

Progesterone function demands normal and harmonious working from all the other neuro-hormonal systems, particularly of the œstrin system. Vitamin E exerts a regulatory action on the progesterone system. In pregnancy chorionic gonadotropin supplements β-gonadotropin in promoting progesterone secretion.

The Adrenocortin System.

The Hormone Complex Adrenocortin. The adrenal cortex secretes a group of hormones, which for the sake of simplicity can be described as constituting adrenocortin. Thus this term (not to be confused with cortin) embraces the sum total of the neuro-hormonal secretion of the systems centred in the adrenal cortex. This method of description has been adopted for reasons of simplicity and clarity.

Adrenocortin, that is, the total hormone secretion of the adrenal cortex, was extracted in part by Hartmann (1928), Stewart and Rogoff and other workers, by fractional extraction of the adrenal cortex with lipid solvents. This extract is termed cortin. Adrenocortin, and thus cortin, were shown to be a mixture of steroids all derived from the androsterone nucleus. They are thus related to cholesterol and the gonadal hormones. These steroids do not represent complete hormones but are nuclei of hormones.

The following steroids have been isolated.

A. The salt corticoids. The principal is desoxycorticosterone. They are related to the electrolyte metabolic factor (or hormone) of the adrenal cortex.

B. The sugar corticoids, such as corticosterone, 11-dehydrocorticosterone, 17-hydroxy-11-dehydrocorticosterone. They are related to the carbohyrate metabolic factor of the adrenal cortex, and are the most effective of all corticoids in maintaining resistance.

C. The sex corticoids (17-corticosteroids). The principal ones are adrenosterone, progesterone, androstene dione, œstrone. They are related to the sexual (masculinising) function of the adrenal cortex.

Adrenocortin considered in its totality possesses the following metabolic regulatory functions.

1. It co-operates in the uptake of oxygen by the cells. This is probably secondary to its maintenance of the optional concentration of electrolytes.

2. It stimulates protein catabolism. This is probably secondary to the action of the sugar steroids, which stimulate gluconeogenesis and thus use protein.

3. It stimulates the release of globulin stored in the lymphocytes.

4. It stimulates gluconeogenesis, that is, production of carbohydrates from protein. It inhibits glycogenolysis and the oxidation of glucose. It is a

diabetogenic, a contra-insulin factor. This is considered as one of the most important functions of the adrenal cortex.

5. It stimulates fat deposition, and its excess causes adiposis. This function is probably connected with the sex steroids.

6. It stimulates retention of sodium, of chlorides and of water, and the excretion of potassium. This is the most important electrolyte function, and is connected with the salt steroids.

7. It contributes to the metabolism of sexual formations, being essentially masculinising. This is a function of the sex steroids.

8. It contributes to metabolism and thus to the function of ascorbic acid.

On the basis of these metabolic regulations the adrenal cortex contributes to the following functions of the organism.

A. It helps the organism to resist all forms of stress. This is primarily a function of the carbohydrate factor. It is the essential organ of adaptation. Its hypofunction diminishes the resistance of the body to all sorts of factors, anoxia, cold, infections, burns, intoxications, fatigue, hæmorrhage, X-rays, and even nervous mental shocks. Hans Selye has recently reviewed his work on the subject.

B. It regulates the blood pressure by stimulating its rise. This is a function of the salt steroids. It reduces capillary permeability.

C. It contributes to the regulation of growth. The mechanism is not clear. On the basis of the maintenance of normal carbohydrate and electrolyte metabolism it allows the normal processes of growth. There is, however, a more specific action which varies with the nature of the steroids. The sex steroids stimulate growth, but according to some authors 17-hydroxy-11-dehydrocorticosterone inhibits growth.

D. It contributes to the regulation of lactation (cortilactin factor) by stimulating lactation. This is a function of the sugar, and up to a certain point of the salt, steroids.

All these factors represent the basic metabolic functions of the adrenocortical hormonal complex. Other functions, however, depend on them. Thus, adrenocortin stimulates basal metabolism, either by direct action or through stimulation of the thyroid. Further, adrenocortin promotes vitamin C storage and through that vitamin or independently plays a certain role in melanin metabolism.

When these metabolisms proceed regularly the various body functions are maintained in balance, particularly immunity, circulatory, digestive and nervous functions. When cortin fails there occur disturbances in these functions, to be studied in connection with Addison's disease.

Construction and Mode of Function of the Adrenocortin System. A cerebral, a pituitary and a glandular centre can be described for this system or system-complex.

The cerebral centre is, like all neuro-hormonal centres, corticohypothalamic, but demonstration of its existence is far from complete. However, certain experiments carried out by Selye show that cortin can be secreted after

peripheral nervous stimulation, and thus imply a central nervous centre. Further, as regards the androgenic factor the occurrence of adrenogenital conditions after hypothalamic lesions can be accepted as proof of the existence of a cerebral centre, although these clinical observations can be interpreted otherwise.

The pituitary centre is composed of those antepituitary cells, probably basophile, which secrete adrenotropin. Its existence is fully proved by the effects of hypophysectomy on the adrenals, and principally by the isolation of adrenotropin and demonstration of its adrenocortical-stimulating action.

The glandular centre of the adrenocortin system is the adrenal cortex or interrenal organ. In man and many other animals it unites with the adrenal medulla to form the adrenal gland. There are two adrenal glands, both situated on the top of the kidneys. They are flat, roughly triangular bodies weighing about 4 grams each. They were described first by Bartolomeus Eustachius in 1563. The cortex as its name implies, surrounds the medulla. Its width is 0·5–1·5 mm.

Phylogenetically the interrenal organ (adrenal cortex) appears first in the cyclostomata. Embryologically it develops from the mesothelium of the Wolffian ridge in common with the ovaries and testes. It is apparent at the 25th day of life in the human embryo.

Histologically it is composed of cells arranged in three rows, glomerulosa, fasciculata, reticularis. In the glomerulosa the cells form round groups about the size and shape of a renal glomerulus. In the fasciculata they form short columns, in the reticularis they group into a reticulum. The cells are polyhedral with round or oval nuclei. They contain lipids, cholesterol with other lipoids and ordinary fat. Like the rest of the adrenal the adrenal cortex is richly supplied with blood. Six times its own weight passes through each adrenal every minute.

According to some authors there exists a special zone in the adrenal cortex for secretion of the androgenic factor (cortigenitalin). This zone, termed the X zone or androgenic tissue, is situated in the innermost layer of the zona reticularis and is composed of small cells, more deeply stained than those of the rest of the adrenal cortex and showing a special biochemical reaction, the Ponceau Fuchsin reaction. The existence of this zone is very debatable.

It is probable that all the systems constituting the adrenocortin system-complex can act from any of their centres. In general they seem to act from their glandular centre, the adrenal cortex activated by the usual mechanism of chemical stimulation. In many cases, however, and particularly in emergencies, these systems can act from their pituitary or cerebral centre. In the latter case activation by nervous stimuli can be considered, as in Selye's experiments.

The Sympathetico Adrenal System.

Construction. The adrenalin or sympathetico-adrenalin system is a typical cerebro-glandular system. Various nervous centres as well as the glandular centre enter into consideration.

The superior cerebral centre, hypothalamic, functioning under cortical control. Its existence has been demonstrated by the experiments of Houssaye and Molinelli, Ransom an co-workers, McLeod. Houssaye and Molinelli place this centre in the lateral hypothalamic area. From this centre nervous fibres descend to the medulla oblongata, where a second centre exists.

The medullary centre. This is situated in the floor of the fourth ventricle and has been demonstrated by considerable experimental work. Tredelenburg observed decrease in the adrenalin content of the adrenal gland after injury to the floor of the fourth ventricle. The experiments of Houssaye, Tournade and his collaborators and many others confirm the existence of this centre, and the diabetes caused by puncture in that region has been shown to be due to adrenalin hypersecretion from the adrenal medulla. Arguments showing that mechanical stimulation of the floor of the fourth ventricle leads to increased secretion of adrenalin have been reviewed by Gellhorn.

After a synapse at this centre, which although determined experimentally has not been localised anatomically, fibres originate and descend to the spinal centre. Experiments involving partial section of the spinal cord indicate that these fibres pass, largely unilaterally, into the ventrolateral column of the spinal cord until they terminate in the spinal centre.

The spinal centre. This is composed of the lateral horns of the VI–XIIth thoracic segments, *i.e.*, by the spinal sympathetic centre which gives rise to the splanchnic nerves. A more precise localisation is impossible, but it is probable that the adrenomedullary centre involves the inferior part of this column.

The existence of this centre is demonstrated :

1. By the continuation of adrenalin secretion after section of the spinal cord at a low cervical segment (Stewart and Rogoff) indicating an independent function of a lower spinal centre. In chordotomised animals sciatic stimulation leads to adrenalin effects which are abolished by denervation of the adrenals.

2. By increase of adrenalin secretion through stimulation of the spinal centres by such substances as strychnine.

3. Principally by increase of adrenalin secretion from the adrenal medulla independently of any change in the blood flow through the gland, after splanchnic nerve stimulation, *i.e.*, stimulation of nerves originating in this spinal centre. Section of the splanchnics diminishes adrenalin output. All this has been demonstrated by important work beginning with Dreyer in 1899 and continued by Tscheboksarow, Ascher, Stewart and Rogoff, and many others.

After a synapse in the spinal adrenomedullary centre fibres emerge and constitute the splanchnic nerves.

The fibres of the splanchnic nerves innervating the adrenal medulla go directly to that organ and are not interrupted in the cœliac ganglia. They terminate around the intramedullary sympathetic ganglionic cells and principally around the phæochromocytes.

The glandular centre, the adrenal medulla. The adrenal medulla develops from the sympathetic ganglia. In the human embryo measuring 17 mm. the primitive cells of these ganglia, the sympathogonia, begin to migrate. Migration is complete in the 85 mm. embryo, at which stage the sympathogonia have taken up their position as the medulla. During migration some of the sympathogonia may split and develop as separate organs at varying distances from the aorta in the region of the renal arteries or the inferior mesenteric arteries, to form the organs of Zuckerkandl.

Sympathogonia are differentiated into two varieties of cell, sympahoblasts which develop into the ganglion cells of the adrenal medulla, and phacochromoblasts which develop into phacochromocytes. Thus at its terminal stage the medulla is composed of these two forms of cell. The phacochromocytes are the important adrenalin-secretory cells. They are the more numerous, are polymorphous, and contain chromophile granules staining brown with chromic acid and its salts.

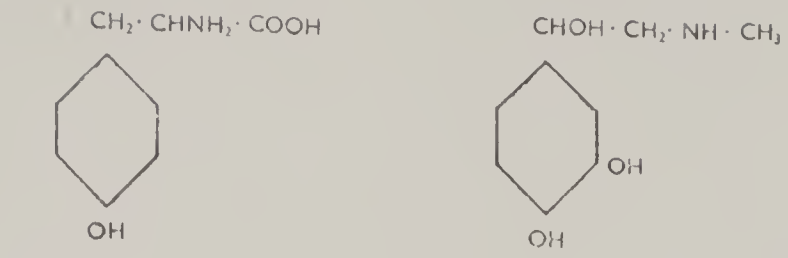
The adrenal medulla is abundant in vessels. They form rich plexuses in the cortex continuous with sinuses situated between the cell groups of the adrenal medulla, which empty into a central vein. It is also richly supplied with nerves, most of them originating from the great splanchnics. The nervous fibres are medullated. They are pre-ganglionic, the medullary cell itself taking the place of the ganglionic cell and post-ganglionic fibre.

Mode of Function. The adrenalin system functions from any of its hypothalamic, medulla oblongata or spinal medullary centres. There is no evidence that it functions from its ganglionic centre, or that it can function independently through its glandular centre. In fact, denervated adrenals do not secrete adrenalin.

That it functions from its hypothalamic and medullary centres has been shown by many experiments. Drugs affecting the cortico-diencephalic centres, such as morphia, camphor, caffeine and guanidine, increase adrenalin secretion. For camphor it has been shown that this effect is not produced if the splanchnics are sectioned. Geiger elicited hyperglycæmia by cooling the blood flowing in the carotid arteries to the brain, and by cooling the brain itself. The effect was absent after splanchnicotomy and therefore appears due to adrenalin. Adrenalin secretion is increased by anoxia, asphyxia, carbon monoxide poisoning, a fall in blood pressure after bleeding or in shock, and insulin hypoglycæmia, and all these factors have a common feature, *i.e.*, insufficient oxidation of the nervous system.

Adrenalin is secreted continuously but more intensively in conditions of stress, both physical and emotional, exposure to cold, asphyxia, hypoglycæmia, anæsthesia, lowered blood pressure. The adrenalin thus poured out stimulates various parts of the nervous system and enables the body to cope more adequately with states of emergency.

The Hormone Adrenalin. This is formed from tyrosine, as comparison of the following formulæ shows.



TYROSIN ADRENALIN

Tyrosine is an aminoacid ingested with food. It is oxidised to dihydroxyphenylalanine or Dopa (Bloch), a compound closely related to adrenalin and transformable into a black pigment resembling the melanin found in the skin. One of the functions of ascorbic acid (vitamin C) seems to consist in stabilising adrenalin, since it prevents its oxidation.

Adrenalin has a permanent and an emergency function.

The permanent action of adrenalin is not accepted by all, but recent work points to its existence, although not to great functional importance. This function is maintenance of the sympathetic nerves in a state of responsiveness, moderate activity, tone. The argument advanced by Cannon against this permanent effect is that adrenalin in small doses induces relaxation of the blood vessels.

The adrenalin system is intermediate between a nervous vegetative and an ordinary neuro-hormonal system. Although adrenalin seems to be secreted continuously it has not the continuous action of most hormones. It acts more like a nervous system element, briefly and intensively when needed. It thus acts in emergencies, including the small emergencies of everyday life. Cannon and his school have shown the emergency function of the adrenal, and Cannon has enlarged this conception to include minor stresses. Adrenalin thus acts in physical and emotional stress, exposure to cold, asphyxia, hypoglycæmia, anæsthesia, fall in blood pressure. It acts similarly to the sympathetic parts of the vegetative nervous system, of which it stimulates various portions and so enables the body to deal more or less adequately with a state of stress or emergency.

In fact, all the following functions of adrenalin occur and are necessary in states of emergency.

1. Adrenalin effects redistribution of blood from splanchnic and cutaneous vessels to the muscles of the heart by causing constriction of the arterioles of the skin and splanchnic vessels (except the intestinal vessels, which are dilated) and vasodilatation of the coronary and muscular vessels. Action on blood pressure is secondary and depends on the quantity of adrenalin secreted by the medulla. As experiments have shown, 0·2 cc. per kilo of a 1 : 10,000 solution produces a vasoconstrictor effect on cutaneo-splanchnic vessels which prevails over its vasodilator effect on coronary and muscular vessels, and thus pressure rises. With a smaller dosage such as 0·01 cc. per kilo of a 1 : 100,000 solution the vasodilator effect on coronary and muscular vessels prevails and

pressure falls. Thus adrenalin is not a regulator of blood pressure, its main biological action being redistribution of the blood, which enables the animal to have more blood in muscles and heart, the organs which fortify it in fight and flight. Its blood pressure effect is variable and constitutes a side action.

2. Adrenalin accelerates the heart, and this, combined with the improvement in cardiac circulation through coronary dilatation, enables the heart to cope with a larger venous return—another important factor in fight and flight. Experimentally certain doses of adrenalin slow down the rate; this, however, is not a direct but a side effect due to the activation of sinus and aortic nerves from elevation of blood pressure.

3. Adrenalin mobilises liver glycogen, promotes glycogenolysis, causes hyperglycæmia and thus provides sugar for the active tissues, the labouring heart and muscles. It also stimulates the metabolism of muscle glycogen, which is important for muscle function.

4. It increases the blood volume, the red cell count and thus the oxygen-carrying capacity of the blood by determining contraction in the smooth muscle of the capsule of the spleen, which is thus allowed to discharge the red cells stored in the interstices of the pulp.

5. It diminishes fatigue of the muscles. The mechanism is obscure although similar to that of the sympathetic nerves. The intramuscular injection of adrenalin increases the animal's capacity to perform work.

6. It increases oxygen consumption, another adaptive mechanism to fight, flight or resistance to cold. Thus the basal metabolism is increased. This is probably effected by means of stimulation of the liver metabolic functions, as it does not occur experimentally after removal of the liver (Soskin). It is not brought about through the thyroid, since it is obtained after thyroidectomy.

It relaxes the bronchial muscles and thus facilitates ventilation of the alveoli.

8. It stimulates secretion of saliva and lacrymation. It does not stimulate sweating in man. It dilates the pupils and closes the sphincters.

Adrenalin acts on some point between the sympathetic nerve endings and the tissue cell (myoneural junction), *i.e.*, at the point where the chemical transmitted, sympathin, is liberated by sympathetic nerve impulses. Its action occurs at neither the sympathetic centre nor the nerve ends, as shown by the experimental fact that its action occurs in the isolated heart, isolated intestine or denervated limb, and that it acts in organs with degenerated nerve endings.

CHAPTER VI

NEURO-HORMONAL SYSTEMS CENTRED ON PITUITARY AND PINEAL

(THE CEREBRAL GROUP OF ENDOCRINE GLANDS)

Pituitary and pineal constitute a special group, topographically the cerebral group, of endocrine organs. They are connected embryologically, the neurohypophysis arising from the nerve tissue of the floor of the third ventricle, the

pineal gland from the roof plate of the diencephalon. The anterior pituitary arises from the nasopharyngeal membrane, but becomes intimately connected with the neuro-hypophysis.

Besides the various endocrinotropins the pituitary secretes certain specific metabolic hormones, which can be regarded as the end-results of the function of particular neuro-hormonal systems possessing a cerebral and a pituitary centre connected by a nervous route. These systems, therefore, are constructed on the cerebro-glandular pattrn. Knowldge of the functions of the pineal gland is very scanty but will be discussed.

The Growth Hormone or Phyone System.

Growth Hormone or Phyone. Secretion of this hormone is the function of this particular part of the neuro-metabolic system. It was isolated from the anterior pituitary by Evans and Long in 1921 and since then has undergone progressive purification thanks to the work of Collip, and of Dingemasse and Freud. It is a proteohormone and has been standardised into rat units, *i.e.*, units based on the growth of rats injected with the hormone. It is secreted ultimately by the eosinophile cells of the antepituitary. Doubt has been raised by Riddle as to the independence of phyone from other antepituitary hormones, and by other authors as to whether phyone is the real effector of the growth system or merely a tropin for a growth factor of the adrenal. For practical purposes the conception of a phyone system can be maintained.

The principal functions of phyone in the organism are the following.

1. Stimulation of the anabolic phase of protein metabolism. Phyone stands in the same relation to protein metabolism as insulin to carbohydrate metabolism. Experimental work shows that injections of phyone cause a positive nitrogen equilibrium and a diminution of urinary nitrogen. Chemical analysis of animals subjected to this hormone shows 25 per cent. more elements than in the controls (Lee and others). In this respect phyone acts similarly to testosterone and contrary to cortin and thyroxin (this, of course, only as regards the end-results, for the various hormones may act on various phases of metabolism). Growth hormone is the typical somatotropic hormone.

2. Stimulation of the metabolic rate of the diaphyso-epiphyseal cartilages and thus of the growth of the long bones (Freud, Levie and others). Under its influence there occurs experimentally proliferation in the cartilage of the epiphyseal disc. Phyone is thus chondrotropic, but its effects are registered not solely by proliferation of the epiphyseal cartilage but also by stimulation of all normal processes of osteogenesis at the diaphyso-epiphyseal junction.

The action on basal metabolism is debated. Most authors, however, hold that growth hormone causes a rise probably through stimulation of the thyroid. Injections of phyone cause hypertrophy of the thymus in animals. It is thus to some extent thymotropic (Uldert and Freud). The significance of this thymotropic action has not been elucidated. At all events the thymus gland is not necessary for action of the growth hormone.

Through its two basic metabolic functions (the protein anabolic and

the chondrotropic) phyone promotes growth.

Construction and Mode of Function of the Phyone System. Two centres, cerebral and glandular, can be described. The cerebral hypothalamic centre is demonstrated by disturbance of growth following hypothalamic lesions, as in some cases of Simmonds' disease, and the experimental production of such disturbances by intervention on the hypothalamus. The glandular centre is situated in the eosinophile antepituitary cells, and is amply demonstrated by arrest of growth following hypophysectomy (Aschner) and by the isolation and study of the growth hormone.

This system functions from either of its two centres. Probably an inherent genetic regulation related to biological rhythm initiates secretion of phyone following a diencephalic impulse. This secretion is continuous from the appearance of the eosinophile cells. It is more intense before closure of the epiphyses, and is increased at certain periods of growth, *e.g.*, before puberty. It continues to act throughout life, however, even although its metabolic result is not, after epiphyseal closure, growth in stature. The nervous and chemical stimuli activating the hypothalamic and antepituitary centres of the phyone system are not known, but normal function of this system depends on perfect environmental, nutritive and endocrine balance. There is a particular antagonism between the phyone and the gonadal systems.

Distinction is necessary between growth and differentiation. Growth is an increase in the number and size of the cells of an organ or tissue, differentiation is the transformation of a homogeneous group of cells into other groups of cells differing in histological and physiological properties. Of growth there is little during the first three months of intrauterine life, but differentiation proceeds intensively. During the last month growth starts. After birth the general growth curve shows four distinct phases; a rapid increase in infancy, especially during the first 3 years, a slow progression between 3 and 12 years, a marked acceleration at puberty between 12 and 15, and deceleration between 15 and 20–21 years, when statural growth stops. Cessation is due to the intervention of other biological mechanisms, such as those promoting union of the epiphyses, the gonadal hormones.

Besides undergoing genetic regulation (genetic impulse and nutritive regulation) growth is governed by the particular state of balance between two opposing systems of force. Growth is stimulated by phyone, an adrenocortical factor, thyroxin and possibly thymus. It is inhibited by the gonadal systems and probably by the pineal and parathyroids. As regards the gonadal system, œstrone in high doses has been shown to inhibit growth. Testosterone in high doses has the same effect, but in smaller doses stimulates the phyone system. The smaller size of the female among mammals may be connected with inhibition of growth by œstrone, and the greater size of the male with stimulation of growth by testosterone.

The Diabetogin System.

This part of the neuro-endocrine system effects secretion of diabetogenin, the diabetogenic hormone of the antepituitary. It is a cerebropituitary system,

its terminal or glandular centre being situated in the anterior pituitary.

The Hormone Diabetogenin. The existence of this hormone has been demonstrated by Houssaye and his collaborators, on the basis of the marked sensitivity to insulin of hypophysectomised dogs and the cure or great relief of the symptoms of depancreatised dogs by hypophysectomy. When anterior pituitary transplants were made in the depancreatised-hypophysectomised dogs (Houssaye) diabetes was aggravated. Evans and his co-workers produced diabetes, *i.e.*, hyperglycæmia and glycosuria in normal animals by injections of antepituitary extracts, and Young produced permanent diabetes by this method. The existence of diabetogenin is proved also by the frequent occurrence of diabetes in acromegalics and patients with basophile adenoma. In fact, the hormone has been isolated, although imperfectly.

Diabetogenin contributes to carbohydrate metabolism by stimulating gluconeogenesis, *i.e.*, production of carbohydrates from proteins, and thus increases the sugar content of the blood. Its excess causes diabetes, its deficiency hypoglycæmia.

Construction and Mode of Function of the Diabetogenin System. Two centres can be accepted, a hypothalamic and an antepituitary. The existence of a hypothalamic centre is partly shown by experiments and clinical observations exhibiting a hypothalamic influence on carbohydrate metabolism. This demonstration is only partial because the hypothalamus may regulate carbohydrate metabolism through other neuro-metabolic systems such as the vago-insulin. However, Weed, Cushing and Jacobson have shown that glycosuria produced by stimulation of the superior cervical ganglion can be prevented by hypophysectomy, indicating thus that this nervous stimulus originating in the hypothalamus is transmitted to the antepituitary. Davis, Cleveland and Ingram have shown that the pathways descending from the hypothalamus, which cause hyperglycæmia when stimulated but, if destroyed, prevent it, run dorsilaterally to the mammillary bodies to the spinal cord centre of the superior cervical ganglion, which when stimulated causes diabetes if the anterior pituitary lobe is unimpaired.

The antepituitary centre is demonstrated by the experiments already quoted, and mainly by the role of hypophysectomy in inhibiting pancreatic hypoglycæmia and glycosuria and the production of diabetes by antepituitary extracts. This proof is more complete since the isolation, with some degree of purity, of diabetogenin from the antepituitary.

The Mammotropin or Prolactin System.

This neuro-hormonal system, beginning in the hypothalamus and terminating in the antepituitary, functions to produce mammotropin, called also prolactin.

The Hormone Mammotropin-prolactin. This hormone was isolated by Stricker and Grueter in 1928 and more completely by O. Riddle and his associates. It has been obtained in crystalline form. It is of protein nature and its chemical constitution is known to a considerable extent. It is usually termed prolactin because of its influence on lactation, but

the term mammotropin seems preferable because of its wider function. Standardisation shows great discrepancies. The usual unit is based on the growth of the crop gland of pigeons, and is known as the bird unit. An international unit is in course of preparation.

Its physiological functions are the following.

1. It contributes to the growth of the mammæ in pregnancy, acting with œstrin and progestin.

2. It initiates lactation after parturition, but only after œstrin and progestin have prepared the mammæ and in conjunction with other neuro-hormonal systems, mainly thyroxin and cortilactin.

3. It is concerned with the maternal instinct. Experimentally it stimulates broodiness in fowls, maternal and paternal behaviour in rats, and nesting behaviour in fish.

4. It inhibits sexual functions, and thus ranks among their regulators. This has been demonstrated in birds but less distinctly in mammals. Continuous administration suppresses the gonadotropic action of the hypophysis with subsequent atrophy of the gonads.

Other physiological functions have been attributed to this hormone but are more open to discussion.

Construction and Mode of Function of the Mammotropin System. This system possesses a cerebral hypothalamic and an antepituitary centre.

The hypothalamic centre is shown by the fact that nervous stimuli, mainly the suction of breast-feeding, causes secretion of milk. This mechanism is analogous to that by which stimulation of the genital tract of certain animals causes secretion of a hormone inducing ovulation. Selye, Collip and Thomson have shown that afferent impulses from the uterus similarly exert an important influence on lactation. All these afferent impulses can act only through a nervous centre and efferent impulses originating in this centre can act only through antepituitary, *i.e.*, neuro-hormonal routes, because purely neuro-vegetative motor impulses do not seem to play an important role in milk secretion, which continues even after complete denervation of the glands. The existence of a hypothalamic centre of mammogenin is demonstrated also by "psychical secretion," some mothers feeling their milk coming after seeing their infant. Herold and Efkerman have shown that stimulation of the breasts by œstrogens (*i.e.*, stimulation of the mammotropin system) does not occur in normal and castrated male and female rats after section of the nerve connections between pituitary and mid-brain. They suggest therefore that œstrin acts by way of the diencephalon, from which impulses reach the pituitary and cause it to secrete the mammary growth factor.

The antepituitary centre is situated in the acidophile cells, and is demonstrated by the suppression of lactation after hypophysectomy. In hypophysectomised cats in particular, although pregnancy is not terminated by the deprivation performed in the later months, lactation does not occur post-partum.

Further, Gructer and Stricker, in 1929, and Corner, in 1930, showed that injection of anterior lobe extract cause hypertrophy of the mammæ and secretion of milk in ovariectomised virgin rabbits. O. Riddle and his school have done much work confirming these experiments and even isolated the hormone mammogenin-prolactin.

The role of œstrin as regulator of the mammogenin system is debated. Experimentally small doses of œstrin stimulate lactation in animals, but larger doses are inhibitory. This is the key of the mechanism. In pregnancy the large quantity of œstrin present in the blood inhibits mammogenic function, and for this reason lactation occurs at the withdrawal of œstrin after parturition. Many authors, however, hold that lactation is inhibited during pregnancy by progesterone or the special œstrin-progesterone ratio. Lactation following œstrin withdrawal is observed in many cases. During fœtal life the mammary glands are exposed to the materanl œstrin, as evidenced by the spurt of mammary growth in new-born infants, and the withdrawal of œstrin after birth explains the " witches' milk " caused by temporary hypersecretion of prolactin. To œstrin withdrawal is attributed also the temporary lactation encountered in castration, menopausis and menstruation.

The Antepituitary Fat Metabolic Factor.

The antepituitary can be regarded as a terminal or glandular centre of other neuro-hormonal systems, with the usual reserve that the term " neuro-hormonal system " is merely a mode of expression, the so-called " pituitary hormones " being usually skeleton keys opening many locks.

There is a fat-anabolic factor, of very obscure nature. Hypophysectomy causes cachexia, and if only the anterior lobe is taken into consideration the pituitary would for this reason possess a fat-anabolic hormone, failure of which after hypophysectomy would cause intensive fat catabolism and thus cachexia. This fat-metabolic factor influences the oxidation of fats. Burn and Ling have shown that administration of a pituitary extract to rats increases the urinary excretion of acetone bodies, and Anselmino and Hoffmann extracted a special fraction from the anterior lobe which, injected into rats, produced an increased concentration of acetone bodies in the blood. The significance of this phenomenon, however, is obscure. It may indicate a slowing of the oxidation of fats, which thus do not pass beyond the ketone body stage. Carel, on the contrary, has found diminution of acetone bodies in the blood following the injection of antepituitary extract.

The Anti-Diuretin System.

The anti-diuretin system is that part of the neuro-metabolic system by which the metabolism, especially the anabolic phase, of water is stimulated.

The Hormone Anti-diuretin. The hormone has not been isolated but is included with other postpituitary hormones in total posterior pituitary extract (pituitrin), particularly in the vasopressin factor.

Its function bears first on water metabolism, for which it is anabolic, *i.e.*, anti-diuretic. It acts on the renal tubules, of which it stimulates the water-

reabsorption function. Some authors maintain that this hormone, secreted in the hypothalamus, inhibits an hypothalamic centre stimulating kidney secretion *via* vegetative nerves. This hypothesis, however, based on certain dubious histological findings, seems somewhat far-fetched.

Anti-diuretin also influences salt metabolism in a manner as yet unknown. Unilateral stimulation or destruction of the nucleus supraopticus causes hyperchloræmia and hypochloruria, and hyperchloræmia is found in some cases of antidiuretin deficiency (diabetes insipidus).

Postpituitary anti-diuretin circulates through the kidney, filters through the glomerules and escapes into the urine, where it is relatively stable and easily detectable.

Construction and Mode of Function. This system possesses a diencephalic and a postpituitary centre.

The diencephalic centre, situated in the supraoptic and paraventricular nuclei of the hypothalamus, has been brilliantly demonstrated by Ransom, Fischer and Ingram. Lesions of this centre cause failure of anti-diuretin secretion by the postpituitary and thus diabetes insipidus. Further, E. Boyd has shown that repeated optical stimuli in the form of brief flashes of light caused diuresis over a period of three hours in albino rats. The reaction did not occur if the eyes of the rats were removed. In the same work Boyd demonstrated that optical stimuli altered the amount of anti-diuretin that could be extracted from the rat's hypophysis.

The diencephalic centre is connected with the postpituitary centre by a nervous tract originating in the supraoptic nuclei, traversing the central wall of the infundibulum and forming a meshwork in the posterior pituitary (Ransom and associates). Experimental lesion of this tract caused failure of anti-diuretin secretion, diabetes insipidus. This has been observed also in a human case of transection of the pituitary stalk, which contains this tract, by Dandy, diabetes insipidus having lasted 11 years in this case.

The pituitary centre is represented by the secretory cells of the postpituitary, the pituicytes, which are highly branched cells having granules in their cytoplasm. Experimentally and clinically lesions of the posterior pituitary cause diabetes insipidus. It has not been shown whether cells of the intermediate lobe of the hypophysis contribute to this centre.

The anti-diuretin system functions from its hypothalamic centre activated by chemical stimuli, mainly the degree of the dilution of the blood passing through the hypothalamus. According to dehydration or superhydration a stimulus depressor or pressor for anti-diuretin arises in the diencephalic centre and is transmitted to the posterior pituitary.

An independent secretion of anti-diuretin by the posterior pituitary has not been demonstrated.

Other Postpituitary Hormonal Systems.

Extraction of the posterior pituitary produces a biological substance called pituitrin. This is a mixture of many factors, of which anti-diuretin is certainly

a special hormone. Of the other biologically isolated factors many, if not all, are probably hormones.

Pitressin. This term applies to that factor of pituitrin acting on the muscular coats of capillaries, arterioles and intestines. Kamm and his co-workers have isolated from pituitrin what they call " pitressin " but this contains not the vascular and digestive pressor factor alone but also anti-diuretin. The last-named factor can be regarded as an impurity in the preparation, pitressin being the pressor factor alone.

Pitressin causes vasoconstriction of the finer capillaries and arterioles in all parts of the body by stimulating their muscular tissue. This is shown by experiments with the complex preparation pituitrin and Kamm's pitressin. The result of injections in man is blanching of the skin, and in some cases elevation of the blood pressure.

Pitressin also causes contraction of the smooth muscles of the intestine, as experiments with pituitrin and Kamm's pitressin have shown. In certain individuals injections of 0·5–1 cc. of pituitrin causes intestinal cramps followed by bowel movements. Pitressin also causes the gall-bladder to empty.

Based on critical reading of the literature, a working hypothesis appears to be that pitressin as defined above (not Kamm's preparation) is a true hormone secrèted by the postpituitary and contributing to the regulation of capillary, arteriolar and musculo-intestinal tonus. Its excess may cause the hyperpiesia occurring in certain toxæmias of pregnancy. Its deficiency may explain the atonic digestive conditions seen in hypopituitarism.

Oxytocin. This factor stimulates uterine musculature. It has been separated from the pituitrin complex by Kamm and his collaborators. Its existence is demonstrated by the occurrence of uterine contractions following injections of pituitrin, noted by Ott and Scott and by Sir Henry Dale. This factor has a direct action, contractions occurring not only in the uterus *in situ* but also in uterine stripes. The pregnant uterus is more sensitive to oxytocin. The effects of oxytocin are inhibited by progestin. Animals with active corpora lutea are refractory to oxytocin and become sensitive when the corpora lutea are extirpated (Knaus).

Oxytocin is probably a true hormone, participating in the balanced hormonal action regulating uterine motility and initiating pregnancy.

Lipoitrin or Lipocatabolin. This factor enters into the pituitrin complex. Its existence has been demonstrated by Raab, who showed that pituitrin injections diminish fat in the blood and increase it in the liver, thus indicating increased mobilisaton of fat from its depots. Lipoitrin is shown also in the work of Keen and Noble, who have produced obesity in animals by removing the posterior pituitary, and pituitrin injections have given some good results in the treatment of obesity.

It is a safe working hypothesis to regard this factor as representing a hormonal secretion from the postpituitary of great importance in fat metabolism.

Construction and Mode of Function of the Post-pituitary Systems. A hypothalamic centre for these hormonal systems depending on the postpituitary analogous to that of the anti-diuretin system has not been demonstrated. Karpens and Peczenik stimulated the hypothalamus and obtained release of a substance in the cerebrospinal fluid capable of producing contractions in uterine stripes, but this experimental contribution is too scanty to be the definite basis of a hypothalamic centre.

According to some authors the postpituitary factors are secreted into the cerebrospinal fluid and the hypothalamus and affect hypothalamic centres. According to others they are secreted into the blood like all other hormones and transmitted to their site of action by a humoral route. The rich vascularity of the postpituitary gives a safe basis for the latter view. Moreover, a humoral route is indicated by the fact that these factors are found in the urine.

The Intermedin or Melanoexpanthin System (Chromatophoroexpanthin).

This system is centred on the intermediary lobe of the pituitary and functions to produce the hormone intermedin or melanoexpanthin.

The Hormone Intermedin. This hormone was reported by Hogben and Winter in 1922 and isolated by B. Zondek and Krohn. It is secreted by the cells of the intermediary lobe.

Its main action is stimulation of the expansion of chromatophore cells in certain cold-blooded animals. In human physiology it is probably related to pigment formation in the retina and thus to optic adaptation (Jores). An influence on water metabolism similar to that of anti-diuretin is possible (Sulzberger). Intermedin passes into the blood, and has been found in the blood and urine of patients with retinitis pigmentosa.

Construction and Mode of Function. The glandular centre of the system is the intermediary lobe of the pituitary which, like the anterior lobe, is derived from Rathke's pouch but lies in close contact with the posterior lobe, which it invests in its anterior surface. If the pituitary is sectioned in certain cold-blooded animals they remain pale even in darkness, *i.e.*, the usual expansion of chromatophores-melanophores provoked by the stimulus darkness does not occur. Bayer observed an individual frog conspicuous by reason of its light colour. Histological examination revealed that a parasite had destroyed the pars intermedia. Injection of an extract of the posterior or intermediary lobe into the lymph sac of a light-coloured frog causes the skin to become dark after a very short space of time. Zondek found a much larger quantity of intermedin or chromatophore principle in the intermediary lobe than in any other part of the pituitary.

The existence of a cerebral hypothalamic centre is amply demonstrated by the opto-pigmentary reflexes. In certain animals light produces pallor, indicating inhibition of the production of melanoexpanthin, and darkness produces black pigmentation indicating stimulation of the production of this hormone. The eel before migration changes into a silver eel, *i.e.*, darkens

(stimulation of intermedin) and at the same time the gonads increase. Both phenomena are produced by conditions of light, and all presuppose the existence of a nervous receptor and effector centre.

The intermedin centre probably functions only from its cerebral centre, which stimulates or inhibits the glandular centre. This cerebro-hypothalamic centre functions through activation by optic stimuli.

The antagonist of this system is the adrenal pigmentation factor, chromatophorocontractin. In darkness a toad is dark, in light it turns pale. If the pituitary is removed the toad remains pale even in darkness because chromatophoroexpanthin (intermedin) is lacking. If the adrenals are removed the toad remains dark even in light surroundings because there is no adrenal melanocontractin. The application of these facts in human biology is not yet clear.

The Pineal Gland System.

Construction. The Pineal Gland. The pineal gland was known to the ancient Greek physicians and was described as "κωνὰριον," a diminutive of a pine cone, and thus translated by Thomas Willis as pineal. In the seventeenth century, Berengaria da Carpi and Thomas Wharton gave good descriptions, and Descartes made this gland the centre of much speculative thought.

This gland belongs to the diencephalon, the important centre of vegetative functions. It is contained in the roof plate of the diencephalon the epithalamus. Three arches develop from this pars epithalamica: (*a*) the paraphyseal arch, which gives rise to an evagination, the paraphysis, glandular in structure, well developed in amphibia and contributing probably to the cerebrospinal fluid and the lateral tela chorioidea or chorioid glands which extend into the ventricles of cerebral hemispheres; (*b*) the postvelar arch, which forms the superior tela chorioidea of the third ventricle; (*c*) the epiphyseal arch, which gives rise to the pineal gland and to a pair of parietal eye-like structures. In certain sluggish animals like the lizard, whose head movements are limited and whose range of vision includes but a limited portion of its horizon, the need for an eye-like structure in the parietal region of the head is clearly apparent, and it is principally in these animals that from the epiphyseal arch a parietal eye develops with a retina, a structure corresponding to the cornea and nervous connections with the posterior commissure. Even in these animals, however, the epiphyseal arch gives rise to a glandular structure, a rudimentary pineal gland. Amphibians show the same features. In animals such as snakes, birds and mammals, however, which do not need a parietal eye, the eye portion of the epiphyseal arch does not develop, and only the glandular pineal portion appears. It is evident from this description that the pineal is not the vestige of the parietal eye but a formation developing from the same part of the brain.

The pineal gland appears embryologically during the sixth week as an evagination of the diencephalon. It may arise in two portions but these merge and develop into the adult organ. This in its contour resembles a pine cone.

Its dimensions vary. The transverse diameter is 4–8 mm., the longitudinal 6–12 mm., the weight 15–25 cg.

Histologically it is constituted by neuroglia and pineal cells with forms transitional between the two types. The pineal cells vary in form and appearance, which accounts for the different classifications given. They are usually large and polyhedral, with a large nucleus around which oxyphil or basophil granules collect, with preponderance of the oxyphil. These cells diminish after castration. They form irregular cords or nests and a rich network of capillaries—the stamp of endocrine gland structure—is connected with them. Pigmented cells also are seen, yellowish in colour and free from iron. Strands of connective tissue from the meninges, including occasional elastic fibrils, invade the gland tissue and divide it into irregular lobes. Concrements of varying size and shape exist throughout the entire gland. These are mainly sand deposits, considered by some as a normal sign of involution but by others as pathological formations. These concretions, through which the pineal may be visualised, appear at about the seventh year. They become more numerous as the years pass, and at 35 are a prominent part of the radiography of the skull. Microscopic cavities with a clear fluid are almost constant at all periods. Larger cysts up to the size of a cherry-stone occur in middle-aged and elderly persons.

Like the adrenals, the pineal is much larger in the fœtus than in the adult. It undergoes involution, which according to Sir James Purves Stewart begins at the seventh year and is complete at puberty. This gland seems very active during the first years of life, as shown by the progressive histological changes detected from the fifth month to the seventh year, by Glibers and Silbert.

Anatomy, embryology and histology thus indicate the pineal gland as a definitely glandular structure necessary in some way to growth and general post-natal development metabolism.

Nervous connections. The work of Laruelle and of Roussy and Mosinger has shed light on the nervous connections and may lead to description of a pineal neuro-hormonal system following the pattern of other neuro-hormonal systems.

The pineal gland, like the pituitary, receives nerves from the diencephalon directly as well as from the superior cervical sympathetic ganglion (Laruelle). These nerves originate from widespread diencephalic centres existing in the epithalamus, hypothalamus and the paraventricular region (Roussy and Mosinger). According to Roussy and Mosinger it is connected also by nervous routes with the pituitary.

Pineal function is elicited by stimuli reaching the diencephalon through the optic and olfactory tracts as well as *via* the cerebro-spinal fluid.

The Pineal Hormones. No hormone has been isolated definitely from the pineal gland. Saphir and, independently, Silberstein and Engel have found œstrogenic substances in the gland, and Hanson has prepared a special extract.

Notwithstanding much recent work the pineal function remains mysterious. It is, however, a seductive working hypothesis to hold that the pineal has an effect on growth and sexual development contrary to that of the pituitary, *i.e.*, an inhibitory influence. The brain would then have in direct proximity two endocrine organs providing the balance necessary for statural growth and sexual development.

An inhibitory action on statural growth has been shown experimentally. Engel, and Rowntree, Clark and Hanson have administered pineal extracts to successive generations of animals and noted dwarfism from the third generation onwards, while Sarteschi, Foa, L. Davis and J. Martin have accelerated growth by means of pinealectomy. However, Dandy obtained no results from pinealectomy, and in some earlier experiments Dana and McCord noted acceleration of growth after administration of pineal extract.

An inhibitory action on the sexual system seems apparent from the experiments of Burger, Fleishmann and Goldhammer, and Engel, who noted inhibition of the œstrin cycle and the neutralisation of pituitary gonadotropin in animals injected with pineal extracts, and from those of Foa, Izawa, Horrox and L. Davis, who obtained acceleration of gonadal development from pinealectomy. However, amid the negative results Rowntree, Clark and Hanson obtained precocious sexual development in their experiments on successive generations.

Clinical medicine offers little information about pineal functions. Acceleration of somatic growth followed by retardation and stoppage, with acceleration of sexual development (pubertas præcox) is seen in pineal tumours, but it is not known whether this is due to hyper- or hypopinealism.

CHAPTER VII

THE PANCREATO-HEPATIC HORMONAL SYSTEMS

(THE UPPER ABDOMINAL ENDOCRINE GROUP)

The neuro-hormonal systems centred on the liver and pancreas can be considered together on account of their embryological and topographical connections. Both are situated in the upper abdomen and both arise from evagination of the primitive duodenum.

The Insulin (Cerebro-Vago-Insulin) System.

Construction. The insulin system may be accepted as constructed on the cerebro-pituitary pattern and thus including a hypothalamic centre, an antepituitary centre (pituitary cells secreting insulinotropic hormone), and a glandular centre. This mode of function, however, seems exceptional. Typically the insulin system is constructed on the direct cerebro-glandular pattern. The connection between cerebral and glandular centres is effected through the vagus, and thus a vago-insulin system can be accepted by analogy with the sympathetico-adrenalin system.

The structure of a cerebro-vago-insulin system is demonstrated by experiments showing that the vagus (beginning at its diencephalic centre) stimulates

secretion of insulin. This experimental proof is ample. Stimulation of the right vagus, which innervates the pancreas, causes hypoglycæmia which does not occur when the pancreatic vein is ligated or when branches innervating the pancreas are sectioned (Britton, La Barre and Vesselovsky, Dietrich). Parasympatheticomimetic drugs such as pilocarpine cause hypogycæmia in the normal rabbit, but fail to produce this effect if the vagi are cut (Clark). A similar finding occurs for synthalin (Zunz and La Barre). Other experiments (Delaune, McLeod, Holt and Ernould) have demonstrated the insulin secretory effect of the vagus, and Holt and Ernould even go so far as to hold that the pancreas by itself does not respond by insulin secretion to hyperglycæmia, this response occurring only when pancreas is connected with the vagus.

The following centres have to be considered.

Diencephalo-hypothalamic centre. This is probably similar to that described for diabetogenin, *i.e.,* localised principally in the paraventricular nuclei. The influence of this centre and of the hypothalamus as a whole on carbohydrate metabolism has already been described, and it is logical to hold that the hypothalamus regulates carbohydrate metabolism not only through the diabetogenic hormone but also through the insulin system.

Medullary centre. This is situated in the floor of the fourth ventricle and corresponds to the dorsal nuclei of the vagus. Puncture of the floor of the fourth ventricle causes hyperglycæmia, which may be due either to the influence of the adrenalin system or to that of the vago-insulin system. The latter causality is shown by a series of experiments demonstrating vagal influence on carbohydrate metabolism and insulin secretion, already delineated.

Ganglionic Centre. From the medullary centre, in which a first synapse is established, nervous fibres descend towards the pancreas. They first reach a parasympathetic ganglion, where the terminal synapse is to be established. This ganglionic centre is formed of the ganglionic cells existing in the organs innervated by the vagus. Ganglionic parasympathetic intrapancreatic cells have been described by Ssobolew and Van Campenhout. From these cells the terminal effector nervous fibres, unmyelinated, arise. They ultimately penetrate the islet and ramify among the insular cells, terminating in free endings among the cells. Gentes and Pensa emphasised the abundance of the nerve supply to the pancreatic islands as compared with the supply to the other parts of the pancreas.

Glandular centre, the pancreatic insula. This was described first by Langerhans in 1869, and after being accepted by Hedon in 1892 as an organ of internal secretion was demonstrated by Laguesse to be the site of formation of the hormone. It is composed of numerous islets of endocrine cells scattered in the pancreas amid the external secretory glandular tissue. Exocrine and endocrine pancreas have a common origin, arising towards the end of the first fœtal month from two buds on the surface of the duodenal anlage.

The islands of Langerhans, islands of solid cells forming the pancreatic insula, are estimated to number between three-quarters and one-and-a-half million. Many of them are connected with the pancreatic ducts but many are

unattached. Their cells are small, cuboid and irregular in shape, two types (A or alpha and B or beta) being distinguished by special staining methods. The B cells, occupying the periphery of the islet, are considered producers of insulin.

Mode of Function. The insulin system may function independently of its glandular centre, the pancreatic insula, through activation by chemical stimuli (increase of sugar in the blood). Some authors reject this independent function.

The insulin system can function from its nervous centres, particularly the superior diencephalic and medullary centres, which can be activated by chemical and nervous stimuli. Increase of the sugar content of the brain seems to be an important chemical stimulus (Etcheverry). Anoxia is another chemical stimulus, causing hypoglycæmia in adrenalectomised animals which is abolished by section of the vagi. The insulin content of the blood of the adrenalectomised rat is increased by exposure to low oxygen (Feldman, Cortell and Gellhorn). Certain physical agents also may act as stimuli. Geiger observed that warming of the blood in the carotid arteries caused a fall in blood sugar provided the vagi were intact, and that the blood of the experimental animals was shown to be richer in insulin when tested on mice. After vagotomy this effect was not obtained. There is such a wealth of experimental demonstration of the possibility of a neurogenic secretion of insulin, fitting in so well with clinical observations, that Gayet's arguments against it should be examined in a spirit of criticism.

The Hormone Insulin. The end-result of the function of this system is secretion of insulin. This was isolated in 1921 by Banting and Best, who thus provided medicine with one of its greatest discoveries. It is a protein of 3,500 molecular weight and high sulphur content (3·2 per cent.) in the form of cystine. It has been obtained in crystalline form.

Insulin has the following functions in the body.

1. It stimulates glycogenosynthesis in the liver and thus promotes glycogen storage. It inhibits glycogenolysis.
2. It stimulates deposition of glycogen in the muscles, a necessity for normal muscular action.
3. It stimulates oxidation of glucose in the muscles.
4. It inhibits glyconeogenesis, *i.e.*, production of sugar from aminoacids.

Lipocaic and other Pancreatic Hormones.

The endocrine pancreas probably secretes hormones other than insulin. Little is known about these hormones and even less about their mechanism of secretion. A direct cerebro-pancreatic structure of these scantily determined neuro-hormonal systems, however, can be accepted as a working hypothesis.

Lipocaic. This hormone regulates fat metabolism. It promotes elaboration of fat in the liver (desaturation and phosphorylation) and probably stimulates departure of fat from its depots (fat depot lipolysis).

When this hormone is deficient, as in pancreatectomy, fat accumulates in the liver. This accumulation, although intractable to insulin, can be prevented

by feeding raw pancreas (McLeod). The preventive action of raw pancreas is not due to its cholin content. Dragstedt, Prohaska and Harris prepared a fat-free alcoholic extract of beef pancreas which, when fed to depancreatised dogs, proved as effective orally as raw pancreas, lecithin and cholin. According to these authors the pancreatic hormone lipocaic is concerned with the metabolism of fat.

There seems to be an antagonism between lipocaic and the fat-metabolic hormone of the antepituitary (lipoanabolin or ketogenin). Injections of the latter hormone provoke infiltration of fat in the liver of diabetic animals, whereas lipocaic administration inhibits this infiltration. Lipocaic is in fact a lipocatabolin. Its deficiency could perhaps explain many cases of obesity.

Wolffe and the Tulasne workers have prepared another fraction from the pancreas, which they term lipopysin and which reduces the cholesterol and phospholipids of the blood. Whether it is similar to lipocaic is not known.

Lipocaic has been used in psoriasis on the basis that this disease includes a disturbance of lipid catabolism. Wolffe's extract has been employed in atherosclerotic gangrene of diabetics where insulin has failed and in which, also, a disturbance of lipid metabolism (cholesterol) is an important factor. The good results in these cases demonstrates also the possibility of a pancreatic hormone stimulating fat catabolism and thus antagonistic to the antepituitary lipoanabolin and synergistic with postpituitary lipocatabolin.

Circulatory Hormone, Vagotonin. In 1929, Professor Gley, working with my one-time assistant at the Evangelismos, Kisthinios, prepared an insulin-free pancreatic extract which, when injected intravenously into rabbits, produced a transitory fall in blood pressure, had vasodilator effects and antagonised the action of epinephrine. Wolff, Findlay and Dessin confirmed the work of Gley and Kisthinios.

This hormone of Gley and Kisthinios has been demonstrated as similar to the hypotensor substance isolated from the urine in 1926 by Frey and Kraut which they called kallikrein and, later, padutin. In 1929, Frey observed that the fluid of a large pancreatic cyst which he evacuated contained a great quantity of this substance, and that in pancreatectomised animals the amount of kallikrein-padutin in the urine decreased as much as 80 per cent.

I have confirmed the results of angioxyl as vasodilator in angina pectoris, endarteritis obliterans and sympathicotonic states.

The specificity of the hormone, however, is debated. It is perhaps similar to Santenoise's vagotonin, a hormone isolated from the pancreas by this author in 1922, which stimulates vagal tonus as adrenalin stimulates sympathetic tonus.

At all events, the pancreas appears to possess a hormone besides insulin antagonistic to adrenalin.

THE NEURO-HEPATIC SYSTEM.

The liver must be considered in any study of endocrine organs, and is in fact the organ to which the conception of internal secretion was first applied by Claude Bernard. Not only does it produce important enzymes (which are

akin to hormones) and even possibly real hormones, but also it is linked closely with the classical endocrine organs, many hormones producing their metabolic effects through action on the liver. It is in reality the most important metabolic organ. In its development it functions at first independently, only later coming under the influence of the vegetative nervous system. It thus follows the structural pattern of the cerebro-endocrine systems but is more a neuro-cellular enzyme system than a true neuro-hormonal system.

The term neuro-hepatic system is here taken to denote the sum total of the neuro-hormonal and neuro-cellular enzyme systems centred in the liver. A separate description of each hormonal and enzyme system possessing this centre is not only impossible in the present state of knowledge but also would be too diffuse.

The liver can secrete enzymes and hormones independently of any hypothalamic influence. There exist hypothalamo-hepatic connections, however, and according to circumstances they intervene in hepatic function. The neuro-hepatic mechanism is one of the most important means by which the hypothalamus and the central nervous system in general regulate metabolism. It must inevitably be considered by the endocrinologist, and neglect of this system in treatises on endocrinology has done great harm to progress in this branch of medicine.

Cortico-hypothalamo-hepatic centre. A cortico-hypothalamic, mainly hypothalamic, centre of the hepatic hormonal and enzyme systems can be accepted. Certain physiopathological considerations on Wilson's disease and on the mechanism of emotive jaundice form an important argument favouring the existence of such a centre.

Recent experiments cited by Henri Brocard, and particularly those of Astanin and Rabel, show that following hypothalamic stimulation hyperglycæmia can be determined *via* a direct hypothalamo-hepatic route.

Experiments by Charles Richet junior and by Dublineau, Ricitelli and Lolli, Astanin and Rabel, Freund and Grafe, indicate the possibility of a central nervous, mainly hypothalamic, regulation of protein metabolism by a direct hypothalamo-hepatic route.

The experiments of Wertheimer, Loewy and Mosonni, Mill, Erben and von Hasselbach point to the possibility of a direct hypothalamo-hepatic influence on the hepatic cells which metabolise fat.

Medullary, spinal and ganglionic centres. The cerebral hypothalamic impulse is transmitted first to medullary, spinal and ganglionic centres belonging either to the sympathetic or to the parasympathtic system. From fibres arising from the terminal sympathetic or parasympathetic ganglia the impulse is finally transmitted to the hepatic cells. In other words, the brain regulates hepatic metabolic functions either through a sympathetic (ultimately the splanchnics) or through a parasympathetic route. The parasympathetic innervation is less important in the liver than the sympathetic.

Via a sympathetic route the hypothalamus causes intensification of glycogenolysis and thus hyperglycæmia. There is thus a hyperglycæmising cerebro-

sympathetico-hepatic system synergistic with the diabetogenin, adrenalin, cortin and thyroxin systems and antagonistic to the insulin system. A cerebro-vago-hepatic system possessing the converse action, *i.e.*, inhibiting glycogenolysis, is not known.

Some authors hold that by a parasympathetic hepatic route the hypothalamus increases urea formation and by a sympathetic route inhibits this formation. This remains in the domain of speculation, however, because of the scantiness and discrepancies of experimental work. But enough is known of the possibility of a cerebral regulation of the metabolic functions of the liver to open new vistas in the understanding of certain metabolic disturbances. It is interesting to recall that a brilliant clinical intuition led Dyce Duckworth to accept a central nervous mechanism for the production of gout. Gout is a disturbance of nucleoprotein metabolism, which is a function of the liver, and it is not irrational in the light of recent work to believe that the central nervous system controls this hepatic function through a direct hypothalamo-hepatic route. It is also possible that metabolic disturbances due to liver dysfunction following a direct cerebral influence are at the basis of many allergic reactions.

OTHER HORMONES.

Endocrinology is no longer confined to the five or seven classical "glands." Incretion is a general function of all cells of the body, and many intermediate forms exist between cellular enzymes acting within the cells, cellular enzymes acting in the immediate vicinity of the cells which produce them, the inductors of the organisers which also act in the immediate vicinity but somewhat more extensively, the local hormones secreted by various isolated or grouped cells and acting within a greater range but always in a certain localisation of the body (sympathin, acetylcholin and the digestive hormones) and finally the hormones secreted by well differentiated endocrine glands.

Local Hormones produced by Nervous Impulses. T. R. Elliott in 1902 suggested that nervous impulses are transmitted through the production of chemical substances. This was demonstrated for the para-sympathetic impulse by Loewy, for the sympathetic by Cannon, and for the cerebrospinal motor impulse by Sir Henry Dale. According to some authors even the synapses in the central nervous system are effected by chemical substances.

Sympathin. This hormone is secreted by sympathetic nerve terminations. Cannon and his collaborators have made important studies on this subject. Sympathin, transmitted to skin and muscles, ultimately produce the sympathetic effect.

Sympathin, although resembling adrenalin (the sympathetic fibres are called adrenalinergic fibres) is not identical with it, as Cannon and Rosenblueth have shown. There are two forms of sympathin. Sympathin E causes excitation and is liberated within structures excited by sympathetic impulses such as the cardiac muscle, liver, vessels, smooth muscle of the skin. Sympathin J is liberated in structures inhibited by sympathetic impulses, such as the intestinal muscles and the coronary vessels.

Acetylcholin. This hormone is liberated by the terminations of certain nervous fibres (hence called cholinergic fibres). It is probably produced by the cells in the neighbourhood of these terminations or at the myoneural junction, under the influence of the nervous impulse. Acetylcholin is the hormonal or chemical transmitter of the nervous impulses. It is produced by (*a*) terminations of parasympathetic fibres; (*b*) terminations of the sympathetic fibres innervating the sweat glands; (*c*) terminations of the sympathetic preganglionic fibres and the ganglionic sympathetic neurones; (*d*) terminations of the motor nerves of the cerebrospinal system.

The action of acetylcholin is inhibited by cholinesterase, a substance produced either by the reacting cells or by the tissue in general. It destroys acetylcholin and thus stops the nervous action. A similar inhibitor for sympathin has not been discovered.

The Digestive Hormones. These are elaborated in the cells of the digestive tube, chiefly in those of the pylorus and duodenum, and are transmitted to neighbouring digestive organs which they govern in their function.

Gastrin (*Edkin*). This is a hormone produced by the cells of the pyloric mucosa. It stimulates gastric gland secretion. Its existence is demonstrated by the experiments of Ivy and Farrell. These authors have autotransplanted in animals a small pouch of the stomach beneath the skin. When an animal so treated is fed, the transplanted pouch secretes acid juice, which shows that feeding produces a certain chemical substance which passes into the blood and stimulates the transplanted pouch.

The pyloric cells are stimulated to secrete gastrin by contact with food.

Enterogastrone. This is a hormone produced by the cells of the pyloric and duodenal mucosa. It inhibits gastric secretion and motility, and is thus an antagonist of gastrin.

Ivy's experiments also have demonstrated the existence of this hormone. In the autotransplanted gastric pouch of the animal, movements (recorded by a balloon inserted in the pouch) and secretion are diminished a few minutes after fat is placed in the duodenum. As gastric motility and secretion are not inhibited when finely emulsified fat or chyle is injected intravenously, this inhibition must be due to a chemical substance produced by the pyloric and duodenal cells when stimulated by fat. This substance is probably enterogastrone. It should be remarked, however, that fat can inhibit gastric motility and secretion by a nervous reflex mechanism, and this interpretation cannot be excluded.

The pyloro-duodenal cells are stimulated to produce enterogastrone by contact with fats. A concentrated solution of glucose or cane sugar has a similar action.

Secretin. This is a hormone produced by the duodenal mucosa and transmitted *via* the blood to the pancreas, which it induces to secrete. It also stimulates bile secretion.

Its existence is demonstrated by the experiments of Bayliss and Starling in 1902, and in fact has been well studied. It was the first incretory product

to be termed hormone and is thus a milestone in the history of endocrinology.

The duodenal cells are activated to produce secretin by contact with acid.

Pancreatic digestive secretion is regulated by the vegetative nervous system as well as by the hormone secretin. According to Mellanby the parasympathetic nerves to the pancreas stimulate the secretion of ferments. Secretin stimulates the secretion of water and the bicarbonate of pancreatic juice.

Cholecystokinin. This is a hormone promoting contraction and evacuation of the gall-bladder and secreted by the duodenal cells.

Its existence has been demonstrated by the experiments of Ivy and Oldberg. Acids and fats, particularly egg yolk and cream, and to a lesser extent meat and proteins, in contact with the duodenum cause contractions of the gall-bladder. As these substances injected intravenously do not cause contractions, this action on gall-bladder motility must be due to a chemical substance produced by the duodenal cells after contact with acids, fats and proteins. Here also a nervous reflex mechanism cannot be excluded but cannot be very important, as stimulation of the nerves of the gall-bladder in cats and dogs produce only a temporary effect.

Through this hormonal mechanism bile is evacuated from the gall-bladder in the course of digestion.

Enterocrinin. This hormone, studied principally by Nassett and his associates, originates in the membranes of the small and large intestines and stimulates the glands of the small intestine to secrete succus entericus.

The Endocrine Spleen. Like many other organs, the spleen possesses endocrine functions besides such functions as the hæmolytic and the fœtal hæmopoietic functions. On the basis of experimental work, although no definite assertion can be made, a cholesterol metabolic factor, an oxidation-inhibiting factor and an iron-metabolic factor can be described.

The cholesterol metabolic factor contributes to synthesis of cholesterol in the body. Splenectomised animals show diminution of cholesterol in their blood, and the normal increase in blood cholesterol 5–6 hours after a meal rich in fats does not occur in them. Further, cholesterol does not increase in the femoral vein after stimulation of the muscles of splenectomised animals.

The oxidation-inhibiting factor, by depressing cellular oxidation, is antagonistic to thyroxin. In many splenectomised rats and particularly dogs, basal metabolism is increased (Danoff). A spleen extract prepared by Schliephake and Maurer has been shown by Ascher and his collaborators to decrease the excitability of the respiratory centre.

The iron-metabolic factor studied by Ascher and his associates stimulates retention in the body of the iron rendered free after destruction of blood corpuscles and disrupture of hæmoglobin. Details of these experiments cannot be given here, but in sum show that iron is increased in the fæces of animals and even man after splenectomy.

Spleen extracts often possess a remarkable effect of alleviation and even cure in certain allergic conditions. There is only scanty material on the endo-

crine function of the spleen up to the present, but undoubtedly this question merits further study.

The Endocrine Kidney. *Renin.* This is a pressor substance found in kidney extracts by Tigerstedt and Bergman in 1878. Recent work based on Goldblat's experimental production of hypertension through ligature of the renal artery permits the view that the ischæmic kidney produces an enzyme-hormone renin, of protein nature, which by acting on a blood globulin produces another substance angiotonin or hypertensin, which causes arterial hypertension through spasm of the arterioles. Renin, thus a pre-angiotonin, is also secreted normally but in small amounts, and explains the rise in blood pressure obtained by Govaerts and Muller by grafting normal kidneys to nephrectomised dogs. Thus the kidney to some extent regulates blood pressure.

Antihormones. Substances arise in the serum of animals treated for long periods with anterior pituitary extracts which gradually render them unresponsive to such extracts. Collip and Anderson were the first to point out this phenomenon, in connection with the thyrotropic hormone. The serum containing these antepituitary antihormones makes other animals, previously responsive to these extracts, refractory.

Antihormones have been obtained from antepituitary extracts, *i.e.,* proteohormones, but not from crystalline purified hormones such as œstrogens, androgens, progesterone, thyroxin and adrenalin. The fact that antihormones have been obtained only from proteohormones or at all events hormones linked with protein, has suggested to certain authors that antihormones are really protein antibodies developed through the usual protein antibody formation.

The question is much debated. The existence of antihormones has distinct therapeutic consequences. Whether it has a bearing on the physiopathology of certain endocrine syndromes is problematic.

CHAPTER VIII

SEX

Sex is one of the most important features of constitution. To understand the natural history of endocrine-constitutional diseases it is necessary to understand the development of sex and the sexual functions.

The sexual characters. All parts of the body bear the stamp of the particular sex to which the individual belongs. All morphological, functional, psychical components of the body-mind differ in man and woman. Of these components a few show a sexual stamp so marked that they are recognised as constituting the characteristics of the particular sex. These are the sexual characters whose conception was introduced by John Hunter and developed later by Charles Darwin. The sexual characters have developed through the particular functions of man and woman in perpetuating the human race and through the need for certain characteristics which promote the sexual appeal of male for female and *vice versa.*

The following table is taken from my "Hermaphroditos."*

SEXUAL CHARACTERS.

MALE.	FEMALE.
Gonadal.	
Testis functioning.	Ovary functioning.
Genital.	
Epididymis, vas deferens, scrotum, penis, urethra of male type (enclosed in penis), seminal vesicles, prostate, rudimentary uterus (prostatic utricle), undeveloped mammæ.	Labia majora and minora, clitoris (rudimentary penis), urethra of female type (perineal or hypospadic), vagina, uterus, tubes, mammæ well developed, parovary, Gärtner's duct (rudimentary Wolffian duct), no prostate or seminal vesicles.
Erections, ejaculation of seminal fluid, rapid orgasm necessary for fecundation, no lactation.	Rudimentary erection of clitoris, no ejaculation, slow orgasm necessary for fecundation, lactation.
Morphological.	
General male appearance, angular and roughly hewn.	General female appearance, round and delicate.
Notable muscular relief, solid skeletal structure.	Muscular relief not apparent, delicate skeletal structure.
Skull large, with well-marked ridges and protuberances. Angular lines. Jaw strong. General expression of physiognomy definite. Canine teeth developed, lateral incisors less developed.	Skull small, with unobtrusive ridges and protuberances. Flowing lines. General expression of physiognomy indefinite. Canine teeth blunt, large central incisors.
Scapular region wide in relation to pelvis.	Scapular region narrow in relation pelvis.
Neck short, with marked muscular and laryngeal relief (Adam's apple).	Neck long and round, without muscular or laryngeal relief.
Lower limbs straight, tendency to genu varum.	Lower limbs converge towards knees, tendency to genu valgum.
Gait energetic and straight, movements vigorous and abrupt, posture erect.	Gait slightly swinging, less vigorous movements, mannered gestures, less erect posture.
Fat localised especially on upper body except for mammæ.	Fat more abundant, localised on lower body but also around mammæ.
Scalp hair short, hair on face and body, upper edge of pubic hair triangular, hair coarse.	Scalp hair long, no hair on face or body except pubis and axillæ, upper edge of pubic hair horizontal, hair fine.

* "Hermaphroditos: The Human Intersex," Heinemann, 2nd Edition, 1946.

Voice.	
Low pitched, baritone or bass.	High pitched, soprano.
Psychological.	
Libido towards women.	Libido towards men.
Instinct of social activity (defence and increase of family).	Maternal instinct.
Activity directed outwards, extravert attitude.	Activity directed towards home, introvert attitude.
Tendency to creative and abstract work.	Work of imitation and precision.
Emotional reactions not very marked.	Emotional reactions accentuated.
Active dominating temperament.	Submissive temperament.
Will to maleness.	Will to femaleness.

Sex Determination. Sex determination is development in the male human being of the male sexual characters, and *vice versa*. It is the result of a complex mechanism consisting in the interaction of (*a*) a biological field or field of individuation; (*b*) a sex-formative impulse; (*c*) a biological environment.

(*a*) The term biological field denotes in terms of energetics a morphological and pre-morphological domain actively organising itself (Waddington). It is thus an aspect of the developing human being, the fertilised ovum, the unicellular organism as well as the embryonic mass. It is a real entity, a system of forces which can be isolated in the living being. This conception, derived from the magnetic field, has developed mainly through the work of Joseph Needham and Charles Waddington, and presupposes biological thinking only in terms of material localisation but also in those of dynamics, of lines of forces. From the point of view of sexual development the biological field of the human embryo, with its power of self-determination, is bisexual. It has potentialities for the development of both male and female characters, and if imagined theoretically to be abandoned to its power of self-determination it would result in a mixture of male and female characters without plan or harmony in the embryo. This bisexual potentiality is transmitted by heredity. On the basis of the self-determination of the biological field certain male and female rudiments develop during the bisexual or undifferentiated phase of the human embryo.

The bisexual field undergoes the influence of two other systems of forces, which contribute to the inhibition of the features of one sex and the stimulation of those of the sex to which the animal will belong. These two systems are formed of the sex-formative impulse and the environment respectively.

(*b*) The sex-formative impulse organises the biological field as a male or female animal. In humans it is always unisexual, stimulating the male potentialities and inhibiting the female potentialities of the field, or *vice versa*. It is manifested in the function of three systems, the genes, the organisers and the endocrines.

The sex genes initiate the sex-formative impulse. Masculinising genes are

contained in the Y chromosome, feminising genes in the X chromosome. Each ovum possesses one X chromosome. Sperm may possess either X or Y chromosome. The fertilised ovum resulting from an X-chromosome sperm, thus an XX fertilised ovum, shows a predominantly feminising genic balance. The XY fertilised ovum shows a predominantly masculinising genic balance and thus initiates a masculinising impulse. The genes, acting through their ferments, masculinise or feminise the cells and thus, up to a point, the organs derived from them. In higher beings, however, complexity has led to development of two other controls, sex organisers and the endocrines.

The sex organisers, *i.e.*, the secondary or tertiary organisers exerting a masculinising or feminising influence on the cells they organise, are the first executives of the sex genes. They continue and develop masculinisation or feminisation of the biological field on the basis of their special endocrine secretions.

The sex endocrines, particularly the gonads, appear as a third group of executives of the sex-formative impulse. They continue throughout life to regulate the sexual characters of the animal. Endocrines are thus only important instruments of the sex-formative impulse, and not the basis of sex formation. A male is a male because he has a masculinising impulse originating in the genes. This initial genetic masculinising impulse causes the formation of masculinising organisers and masculinising endocrines. Thus a male has a testis because he is a male, but is not a male because he has a testis. Woman is not the appendage of her ovaries, as stated in Virchow's famous dictum, but has ovaries because she is a woman.

The endocrines, more especially the gonads, secrete masculinising or feminising hormones through which the sex-formative impulse continues and develops in embryonic and post-embryonic life. The masculinising hormones are testosterone from the testis, corticosterone and possibly other androgens from the adrenal cortex, and progesterone from the ovaries. Feminising hormones are the ovarian œstrogens, antepituitary prolactin and possibly, in part, thyroxin. Both groups of hormones are found in all humans, male and female, and in the last resort it is predominance of one or the other group that makes for masculinisation or feminisation. This mechanism of sex determination is ultimately a matter of balance—balance of hormones, of organiser inductor secretions and of sex genes.

(*c*) Environmental factors also act on the biological field (and at the same time on the executives of the sex-formative impulse) and constitute either a masculinising or a feminising force. This is shown by various experiments with lower animals, cited in my "Hermaphroditos." In humans the only environmental factors to be considered are the social, educational and psychological environments. When this environment is suitable, masculinisation in genetic males and feminisation in genetic females is promoted.

Disturbances in Sexual Development, Intersexual Conditions.

When this mechanism of sex determination is disturbed, when for instance the

masculinising impulse is weak, the female potentialities of the field are imperfectly inhibited and the male potentialities can develop only imperfectly. The living being is a male genetically but shows imperfect development of certain male sexual characters and the existence of certain female characters, and is a male intersex. Through a similar mechanism a female intersex, through a weak feminising impulse, develops from a genetic female.

The mechanism of sex determination can be disturbed either at the genetic-organiser phase of development or at the endocrine phase. In the first instance we have to do with deep constitutional intersexes, in the latter with endocrine intersexes.

Intersexuality is a normal phenomenon. There is no such thing as a perfect male or a perfect female. Every male has certain female features, and *vice versa,* as Darwin pointed out. The field is always bisexual, and even a normal genetic unisexual impulse cannot inhibit all heterosexual potentialities. The intersexes seen in medical practice represent exaggerations of a normal process.

The pathological intersexes, which are either male or female, correspond to various degrees of intersexualisation. In morphological intersexuality (feminism and virilism) intersexualisation bears on the morphological and psychological sexual characters. In genital intersexuality (the old pseudo-hermaphroditism) intersexualisation involves the genital sexual characters. In gonadal intersexuality (the old "true" hermaphroditism) intersexualisation involves also the gonads.

Experimental application of an intersexualising (feminising) process in a male animal results in three different degrees of intersexuality. In the first degree, the mildest form, the extra-genital, mainly the morphological, characters are feminised, genital organs and gonads remaining male. In the second degree the feminising process involves also the genital organs. In the third degree the gonads themselves are feminised, and thus the genetically male experimental animal possesses ovarian tissue as well as testes.

DISEASES OF THE THYROID, PARATHYROID AND THYMUS GROUP

CHAPTER IX

THE GOITRES

The term goitre indicates two not absolutely identical pathological processes found in general endocrine pathology; the process of simple hyperplasia, here involving the thyroid tissue, and the process of endocrine adenoma, here thyroid adenoma. Diffuse hyperplasia constitutes the condition termed diffuse goitre, parenchymatous at origin, later colloid and cystic. Thyroid adenoma constitutes the condition known as nodular goitre. Much of the confusion in the pathology and clinic of goitre can be avoided if this disease group is viewed in the light of the general principles governing endocrine pathology.

DIFFUSE GOITRE (PARENCHYMATOUS, COLLOID, CYSTIC), THYROID HYPERPLASIA

Physiopathology. Diffuse thyroid hyperplasia constituting diffuse goitre arises from an intensive diencephalo-pituitary drive and represents a total hypersthenic reaction of the thyroid system. An abnormal stimulation of the diencephalic centre of the thyroid system causes hypersecretion of pituitary thyrotropin, and this in turn causes thyroid hyperplasia. Experimentally thyroid hyperplasia has been produced by injections of thyrotropin (pituitary thyrotropic hormone).

The first phase of the thyrotropic hormone drive results in a diffuse or circumscribed parenchymatous hyperplasia, and when arrested at that stage the goitre is called parenchymatous. The follicular epithelium passes from low to high cuboidal, and even columnar. Infoldings and even plications of the lining epithelium appear, and instead of the smooth outline one of considerable irregularity with papillary infoldings develops. The intrafollicular colloid becomes scarce and later disappears—an important point. Thus the thyroid enlarges, because the parenchyma extends and the vessels develop but the colloid diminishes or disappears.

Later there is retrocession from the parenchymatous phase. The colloidal iodine building store is restored and accumulates in the acini to excess, and the gland therefore enlarges and gains in firmness. Through distension of the acini by colloid the columnar epithelium shrinks to cuboidal and finally to flat cuboidal. Cysts are produced when colloid accumulates in great quantity. The vascularisation of the gland diminishes. When arrested at this stage the goitre is termed " colloid," and may be " cystic."

This hyperplastic process may involve the aberrant thyroids, and when these are involved to the exclusion of the principal thyroid the condition is an aberrant goitre.

This increased thyrotropin secretion occurs as a reaction to a thyrohormone (or thyroxin) deficiency. In the experimental goitres determined by thiouracil and allied substances, as also by thiocyanates, thyroxin deficiency occurs because these toxics inhibit thyroxin formation in the thyroid.. In iodine deficiency goitre thyroxin deficiency occurs because of insufficient material for its production. In certain metabolic disturbances, as for instance in the endocrine shocks of puberty, thyroxin is produced in normal quantities which, however, are inadequate for the greater demands of the organism. There occurs thus a relative thyroxin deficiency. Certain toxics may act also through tissue asphyxia, as accepted by Marine in methylcyanide (cabbage) goitre. Thyroxin is produced normally, but as these toxics disrupt the oxidation systems of tissue cells the thyroxin cannot act and thus, here also, is blocked. Through the hyperplastic reaction hypothyroidism is usually avoided in goitre.

A special reactivity of the thyroid cells, a special mode of function of their cellular enzymes, is an important factor in the production of hyperplasia without hyperfunction, that is, of simple goitre.

Etiology. Clinically many goitres show definite etiological factors. These are iodine deficiency, thiocyanate intoxication, gonadal disturbances. All other goitres are cryptogenetic, *i.e.*, no definite etiological factor determining the diencephalo-pituitary hyperplastic thyroid drive can be detected.

Iodine deficiency is the predominant etiological factor in endemic goitre, and possibly in some sporadic goitres. Endemic goitre is a particular form of a deep constitutional disease to be described later, cretinism. The etiological role of iodine deficiency in these cases has been demonstrated by iodine deficiency in the food and water of endemic goitre regions, and by the prophylactic role of iodine.

Thiocyanate intoxication has been demonstrated as a factor of goitre following thiocyanate administration for treatment of hypertension. The role of gonadal disturbances is demonstrated by the occurrence of goitre at puberty (often transitory) and at menopausis.

Clinic. Two phases can be distinguished in the clinical history of patients with diffuse goitre, the morphological and the pressure phases.

In *the morphological phase*, at which the goitre is usually arrested, the only manifestation is the thyroid tumour. There are no symptoms except those caused by the anxiety of the patient and the depression induced by his deformity. The enlarged thyroid is perceptible on inspection and on palpation. It moves on deglutition. Auscultation reveals in some cases a to-and-fro bruit. Percussion of the upper chest, and principally radiological exploration, show the thoracic component of the goitre. The goitre may involve an aberrant thyroid, and can thus be found as far distant as the outer border of the sternomastoid and even the external end of the clavicle. Goitre involving a thoracic aberrant thyroid is of great clinical importance.

Diffuse goitre can be arrested, after increasing gradually, at this morphological stage and persist throughout life. In other cases it may diminish and disappear, as do some goitres of puberty. In a third group of cases it passes into the second or pressure phase.

The pressure phase follows the downward growth of a cervical goitre (goitre plongeant) or may manifest the development of an undiagnosed goitre involving a thoracic aberrant thyroid.

Diffuse goitres can descend into the thorax through their lower pole. Intrathoracic goitres can reach enormous proportions.

Pressure bears principally on the trachea, which is narrowed and deviated, and on the internal jugular veins, which are thus impeded in their function of draining the blood from the head and neck. These constitute the essential disturbances in pressure goitre and determine its clinical manifestations. More rarely pressure is exerted on the larynx, the recurrent laryngeal nerve, the subclavian veins and, exceptionally, on the sympathetic or the vagus.

The onset may occur through a sudden paroxysmal attack of dyspnœa, but in most cases is manifested by mild and progressive dyspnœic symptoms. As these may occur in individuals with an undiagnosed intrathoracic goitre, it is

obvious that goitre must be considered in the differential diagnosis of dyspnœa, whether paroxysmal or progressive.

The complete syndrome manifesting pressure goitre is made up of dyspnœa, cough, voice changes, palpitations and tachycardia.

Dyspnœa is the leading symptom. It may simulate an asthmatic attack, thus giving rise to many errors in diagnosis. It is often very violent, and cases have been described of patients brought to hospital for an acute suffocative attack often misdiagnosed (as in the case reported by Joll, in which the patient was sent to a fever hospital with the diagnosis of croup) and relieved by operation on the goitre. A distinctive feature in intrathoracic goitre is the occurrence of attacks during sleep, because whereas during consciousness the head and neck are held in a position which makes breathing easy, this muscular vigilance is relaxed during sleep and attacks of suffocation are provoked. Stridor, usually inspiratory, may accompany pressure goitre dyspnœa when there is bilateral tracheal compression.

Cough is a frequent finding, and is due either to bronchitis caused by the bronchial stasis resulting from thyroid pressure or to tracheo-bronchial and nervous pressure. In this last case it is dry, tiring and spasmodic, is often associated with paroxysmal dyspnœa, and is aggravated during sleep. Voice changes are rarer, and they also may be due to the laryngitis and bronchitis described above, to direct pressure on trachea and larynx, or to involvement of the recurrent nerve. They consist in unaccountable breaks in the voice, weakness of the voice, or a croaking harsh voice.

Palpitations and tachycardia complete the picture. They are due to dyspnœic phenomena, and exceptionally to nervous sympathetic pressure. They constitute the mechanical "Kropfherz" of Rose, and should be distinguished from the thyrotoxic cardiac manifestations such as occur in toxic goitre (Leon Bernard and Cawadias). Attacks of bradycardia due to pressure on the vagus have been observed (Joll). Pressure on the internal jugulars cause disturbances of circulation in neck and head. The veins in these regions are distended, giddiness may occur, and in some cases swelling œdema of the neck and face develop. Dysphagia also is seen from pressure on the œsophagus or vagus.

Pure diffuse goitre does not develop towards thyrotoxicosis or cancer. It should be remembered, however, that in many diffuse goitres nodular formations coincide, and thus for practical purposes such complications have to be considered.

Diagnosis. Simple morphological goitre is easy to diagnose except in the rare cases of asymptomatic intrathoracic goitre detectable only by radiology. The only delicate point is differentiation between the simple goitres of nervous individuals who show anxiety symptoms, intolerance of pressure on the neck, emotive palpitations and tachycardia on effort, from Graves' disease with diffuse goitre.

The diagnostic problem offered by pressure goitre is more delicate. The importance of considering intrathoracic goitre, even in the absence of cervical

goitre, in all cases of dyspnœa, should be stressed again. A few such cases are diagnosed as asthma, as in the classical case of Charles, whose life-long "asthma" was cured by surgical removal of an intrathoracic pressure goitre.

Cancer of the thyroid is another stumbling-block, although mistakes in diagnosis are not of great practical consequence because in both diseases thyroidectomy is indicated. In cancer the thyroid is more painful, more indurated, more adherent to surrounding tissues, and thus nearly immobile on deglutition. There is distinct lymphatic involvement.

Differentiation from toxic or cardiotoxic goitre is another problem. Here, however, the cardiocirculatory symptoms predominate and are nearly specific. Tachycardia and palpitations dominate even dyspnœa. Basal metabolic determination is not helpful, as it is often normal in cardiotoxic goitre. Diagnosis is often very difficult, and cases of cardiotoxic goitre were described as pressure goitre (Rose's Kropfherz) until Leon Bernard and Cawadias pointed out their thyrotoxic origin.

Certain thyroiditis also enter into the differential diagnosis. These are tuberculosis of the thyroid, syphilis, lymphadenoma, Riedel's disease or ligneous thyroiditis, Chaga's disease or tropical thyroiditis, and Hashimoto's disease, a lymphocytic infiltration of the thyroid which does not give rise to much swelling. The concomitant symptoms in all these diseases help in the differentiation. When there exist no concomitant symptoms of a more general disease, as for instance in Riedel's disease, differentiation becomes a matter of impression. The important point is, whether the thyroid tumour causes pressure or not. Radiological exploration is of the greatest help.

Therapeutics. When a simple goitre is not very deforming, or when the patient is pusillanimous and prefers to keep his deformity, operation can be avoided or deferred provided the case is thoroughly supervised. The same consideration applies to the goitres of puberty, and up to a certain point to the simple goitres of the climacteric, stringent supervision not being necessary in these cases.

Internistic treatment should be applied in such cases. This consists first of all in certain general constitutional measures to improve the general health. Adequate diet, good hygiene, correction of digestive disturbances, sedation or tonification of the nervous system according to indications, often give excellent results. Iodine is the chief medical agent. It should be given only for short periods, with long intervals between them, and in very small doses. I prefer the homœopathic dilution (6x) as the dangers of aggravation through iodine, and of production of a toxic goitre, are very real. This is one more reason for placing great reliance in such cases on general constitutional measures.

For pressure goitre thyroidectomy is the only treatment. Some authors advise against operating during an acute attack, but Joll describes successful results during such emergencies.

THYROID ADENOMA, NODULAR GOITRE

Physiopathology. The physiopathology of nodular goitre, *i.e.*, of thy-

roid adenoma, is less clearly known. The coincidence of nodules of adenoma in cases of diffuse thyroid hyperplasia probably points to a similar origin, but altogether the physiopathology of thyroid adenoma, as of all endocrine adenomas and other tumours, remains a mystery.

Like all endocrine adenomas, thyroid adenoma may be endocrinic or non-endocrinic. In other words, it may or may not secrete thyroid hormone in excess. The present concern is the non-endocrine, *i.e.*, the non-toxic variety. The endocrine variety, "toxic adenoma," is described with the hyperthyroidisms.

Thyroid adenomas vary in dimensions from that of a pea to that of a tangerine or even larger. They may be multiple. They are definitely encapsulated. They are composed of thyroid cells, arranged at first like those of the parenchymatous goitre and, through the same mechanism, showing colloid formations or cysts. They develop in the thyroid gland itself, but also in ectopic thyroids, and are thus encountered at the root of the tongue, retrosternally or at odd sites in the cervical region.

Thyroid adenomas, nodular goitres, are usually encountered after adolescence, and their frequency increases with age. They are more common in females. Altogether they are fairly frequent and routine examination reveals them in many patients who consult for other diseases. M. J. Schlesinger and his co-workers found them in 8·2 per cent. of individuals in a non-goitrous region.

As the physiopathology is obscure the etiology is unknown.

Clinical History. Like all endocrine adenomas, nodular goitres may be latent during the whole life of the patient. When voluminous they may cause pressure symptoms. In some cases they become toxic, *i.e.*., endocrinic. In others they undergo cancerous degeneration.

Latent nodular goitres are easily detected on palpation, or even on inspection if they are voluminous. Thyroid adenomas in the thoracic portion of the thyroid are detected by means of X-rays.

Pressure nodular goitres are manifested by the syndrome of pressure goitre already described for diffuse goitre.

Endocrinic or toxic nodular goitres (adenomas) are described with the hyperthyroidisms.

Malignant degeneration should be considered with care by the clinician. It does not occur from a diffuse goitre, and when it occurs in an individual known to have a diffuse goitre it originates in a coincident adenomatous nodule.

In fact, cancer of the thyroid usually arises from a previous adenoma, a nodular goitre. Only in 10 per cent. of cases does it develop from a previously healthy thyroid. It can be stated that 2–3 per cent. of simple goitres (including diffuse hyperplasia as well as adenoma) undergo malignant degeneration. This gives an idea of the extent to which nodular goitres are subject to malignant degeneration.

The history is characteristic. The thyroid adenoma, isolated or coinciding with a diffuse thyroid hyperplasia, has been quiescent for years when it starts

developing with some rapidity. As the origin of the malignant neoplasm is an adenomatous nodule, the enlargement of the thyroid appears more localised at onset. The thyroid tumour at once becomes harder and cannot move freely over the trachea and larynx. Severe symptoms develop, and amongst them dysphagia more marked than in non-cancerous pressure goitre. Thyrotoxic symptoms may make their appearance, the general condition becomes very bad and metastases end the drama.

Diagnosis. There is no great difficulty in diagnosing simple " morphological " adenoma except when it develops in an aberrant intrathoracic thyroid. Diagnosis of pressure nodular goitre follows the lines indicated for pressure diffuse goitre. Diagnosis of toxic or endocrine nodular goitre is dealt with elsewhere. A few words should be said on diagnosis of nodular goitre degenerating into cancer of the thyroid.

This diagnosis is often difficult. In Pemberton's statistics malignancy was suspected in only 35 per cent. of cases before operation. The important point is to catch the moment at which a benign simple growth becomes malignant. The history of the patient will help, but the problem of the small thyroid nodule that becomes a little harder, a little larger and slightly more painful is nearly insoluble.

Differentiation from pressure goitre has been described already with that disease. Differentiation from toxic goitre also is easy if the characteristic cardiac manifestations of that condition are borne in mind. I have not seen a toxic goitre become malignant, a finding that coincides with the experiences of those, such as Means, who have seen more goitres.

Differentiation from various chronic thyroiditis is both difficult and important, because an extensive operation is not necessary in such thyroiditis. Riedel's disease or ligneous thyroiditis engenders the greatest difficulties. Characteristic differential signs in favour of this disease are extreme hardness, regularity of surface, marked diffusion of the limits, involvement of the gland *in toto,* rapid development in a young man without previous goitre. It should be remembered that growth in malignant goitre does not involve the entire gland at first because it starts from a nodule. Riedel's disease is relatively rare. Biopsy may help.

Hasimoto's disease or lymphatic struma is even rarer. It does not give rise to an important growth. Chronic Chaga's disease, which according to Chaga is due to infection by Schizotrypanum Cruzi, is confined to Brazil and Venezuela, and its existence has even been doubted lately by G. Valerio. Tuberculosis, syphilis and lymphadenoma of the thyroid are differentiated by the concomitant symptoms.

In all these cases the rule should be " in doubt do not abstain " from thyroidectomy.

Therapeutics. The therapeutic problem in nodular goitre (thyroid adenoma) is more complex than in diffuse goitre (thyroid hyperplasia). The only danger to individuals with diffuse goitre, and thus the only indications

for thyroidectomy, are the unsightliness and the possibility of development of pressure symptoms and thus expectant treatment is often permissible. In nodular goitre, however, there exists the same danger of possible pressure symptoms and also the danger of development of toxic symptoms and, principally, that sword of Damocles, cancerisation. Theoretically it would be safer to remove all nodular goitres, but as these are extremely frequent and often of difficult diagnosis this is not possible, and every case must be judged by itself on the basis of the general principles delineated. Intrathoracic nodular goitres are liable to cause severe pressure symptoms. Nodular goitres in general must be watched for toxic symptoms, and above all the nodular goitres of aged persons must be watched for cancerisation.

CHAPTER X

GRAVES' DISEASE

(PARRY-GRAVES' DISEASE, BASEDOW DISEASE, EXOPHTHALMIC GOITRE, THYROTOXICOSIS).

The hyperthyroidisms constitute a disease group isolated on a common physiopathological basis, hyperfunction of the thyroid system. This group includes Graves' disease, which is a cerebro-pituitary hyperthyroidism, and toxic nodular goitre or toxic adenoma, which is a primary thyroid or neoplastic hyperthyroidism.

The symptom complex corresponding to Parry-Graves' disease was first detected by Caleb Hillier Parry in 1786 although reported only in 1825, and described more accurately by Graves in 1835.

The condition was named Graves' disease by the great French clinician Trousseau in 1840. The Italians call it Flajani's disease, the Germans Basedow disease; but Flajani mentioned goitre and exophthalmos somewhat superficially in one of his works in 1830, and Basedow simply added in 1840 some symptoms to the already full clinical studies of Parry and of Graves. The disease is known by many synonyms aiming, unsuccessfully, at symbolising its physiopathology and clinic. An example is hyperthyroidism, which has the defect of being too comprehensive, as it includes not only cerebro-pituitary hyperthyroidism, the basis of Graves' disease, but also the hyperthyroidisms symptomatic of certain pituitary tumours (pituitary hyperthyroidism) and those determined by a hypersecreting thyroid adenoma (toxic adenoma, primary thyroid hyperthyroidism). The term thyrotoxicosis is liable to a similar criticism and the expression exophthalmic goitre must be rejected because there are cases of Graves' disease without exophthalmos and without goitre. The term Graves' disease, or more accurately Parry-Graves disease, is best. It is justified historically (whereas the terms Flajani's disease and Basedow disease have no such justification) and it has the great advantage of not presuming on a physiopathology, which has changed since the days of Graves and may change to-morrow, while the clinical syndrome remains permanent.

The clinical syndrome described by Parry and by Graves was first linked

with functional disturbances of the nervous system, but in 1884, Rehin, and two years later, Möbius, accepted thyroid hyperfunction as the physiopathological basis of the disease. Contemporary work combines the nervous and thyroid conceptions by holding that the hyperthyroidism of Graves' disease originates in an abnormal diencephalic impulse leading to hypersecretion of antepituitary thyrotropin and thus to a secondary hypersecretion of thyroid hormone by the thyroid cells. A local factor of thyroid cellular reactivity intervenes, and the continuous diencephalo-pituitary drive does not allow of the moderation of thyrotropin which normally occurs when the thyrotropin level in the blood rises. That Graves' disease is a cerebro-pituitary hyperthyroidism is demonstrated by the role of emotional factors in its genesis, its occurrence in some cases after encephalitis, its improvement with hypothalamic sedatives and various other clinical and experimental facts found in the work of Falta and of his pupils Fenz and Risak. This conception complies with modern knowledge of neuro-endocrine connections.

Thyroid hyperfunction is manifested by certain morphological features. The thyroid is enlarged (goitre), the enlargement being uniform or involving principally one lobe. Microscopically the amount of secretory tissue is increased. The cuboid epithelial cells of the follicles become columnar and more numerous, show increased mitochondria and the intra-follicular colloid disappears. This intense cellular proliferation, combined with the disappearance of the intra-follicular colloid, causes papillary infoldings modifying the lumen of the follicle. The lymphocytes of the thyroid multiply, constituting lymphocytic foci in some parts. The iodine content of the gland diminishes to one-tenth or one-fifteenth of its normal quantity, and sometimes falls to zero.

Hyperthyroidism is not the only element in Graves' disease. As in all constitutional diseases, the balance of the entire system of constitutional regulation has been broken, and thus besides the thyrohormonal system other constitutional regulators are involved. The gonads are often depressed. The thymus is enlarged in about 79 per cent. of cases (Capella). The adrenal cortex is depressed. The adrenalin system, on the contrary, enters into hyperfunction. The sympathetic component of the neuro-vegetative system is stimulated in some parts but over-stimulation of the parasympathetic component is observed in other regions. This is only a broad outline of the disturbances of the other elements of the constitutional regulators system. There is no absolute rule.

The imbalance of the system of constitutional regulation with predominance of hyperthyroidism disturbs body chemistry extensively. Above all, the rate of cellular oxidation is increased and the candle of life burns intensely. Basal metabolism is increased by 25 per cent. in mild cases, by 20–40 per cent. in moderately severe cases, and by over 40 per cent. in severe cases. Water catabolism is increased, and the patient becomes dehydrated. In some cases, however, water is retained instead of being lost with the consequences of pulmonary and cerebral œdema and œdema of the orbital tissue, which may explain exophthalmos. Protein catabolism is increased, resulting in protein loss

within the body. Glycogenolysis in the liver is exaggerated, with the result of excessive sugar production and thus hyperglycæmia and glycosuria. Fat catabolism also is increased. The fat depots empty themselves of their fat and cholesterol diminishes in the blood. Minerals such as calcium also are lost to excess. Altogether the two basic metabolic disturbances, exaggeration of the rate of oxidation and of water loss, cause intensification of all catabolic functions.

An important metabolic disturbance refers to iodine. In Graves' disease the thyroid absorbs iodine with avidity but uses it immediately for production of thyroxin and stores none. Thus the iodine content of the Gravesian goitre may be as low as 3 mg. compared with the 10 mg. of the normal thyroid. As the thyroid in Graves' disease gives away immediately the thyroxin stored in excess, blood iodine is increased (27 γ per cent. instead of the normal 8–20 per cent.). Excess of iodine in the blood means an excess of iodine in the urine, where much more than the normal 72–343 γ found in non-goitrous regions is encountered. The essential disturbance of iodine metabolism in Graves' disease is a defect of storage in the thyroid, demonstrated also by the fact that ingestion of iodine in Graves' disease does not bring about an immediate increase in iodine excretion, because the ingested thyroid is trapped by the avid thyroid gland. Later, however, iodine is excreted in excess (iodine tolerance test).

As all functions of the body-mind depend on the perfect working of the biochemical processes, disturbance of these processes by hyperthyroidism reacts on these functions.

Growth is intensified, because growth means multiplication of cells, and multiplication of cells depends largely on oxidative processes. Differentiation is intensified—a much more distinct repercussion of oxidative increase.

The central nervous system becomes more active and irritable because its metabolism is increased. Intensification of the skin metabolism is manifested by increased perspiration. The cardiovascular system responds to this increased metabolism by intensifying its work—hence tachycardia. The digestive system shows increased irritability for the same reason. Exophthalmos is determined not by excess of thyroxin but probably directly by excess of thyrotropic hormone.

All these organic repercussions constitute the clinical picture of Graves' disease and will be studied in more detail with the clinical history.

Etiology. Graves' disease in its mild form is extremely frequent. In its complete form it is also of high incidence, particularly in women (85 per cent. of cases, according to the Mayo Clinic statistics). It is a disease of the adult, although rare cases have been described in children, and mild forms occur in women at the climacteric phase. It is met in all regions of the globe, and notwithstanding certain authors does not seem more frequent in regions of endemic goitre. Jews and Latins are the most susceptible. Negroes, notwithstanding their frequent simple goitre, are not very prone to Graves' disease.

It is determined by a series of environmental factors acting on an individual

born with a genogenically labile thyroxin system. This constitutional genogenic factor is demonstrated by the familial and hereditary nature of the disease, and by the occurrence of Graves' disease in individuals showing special personality traits constituting the hyperthyroid biotype. The environmental factors which, acting on this inferior thyroxin system, determine Graves' disease, are psychogenic, infective, toxic, traumatic, tumours pressing on the diencephalon and other endocrinopathies.

The importance of psychogenic factors is recognised nowadays, and their influence is explained by the cortico-diencephalic connections. Conscious and subconscious conflicts, chronic worry, sudden catastrophes, frightening experiences have been noted often in the etiological constellations of such patients.

Infective factors act through their diencephalic localisation, and their role is demonstrated by the frequent association of Graves' disease with post-encephalitic Parkinsonism and by the occurrence of Graves' disease following epidemic encephalitis. As this encephalitis, as well as other virus infections with a diencephalic localisation, may occur without strident clinical manifestations, it is possible that latent encephalitis is the origin of many cases of Graves' disease in which no definite etiology is found. Focal infections, particularly those involving tonsils and adenoids, also act, probably through the mechanism of diencephalic localisation. The role of tuberculosis is problematic. It was stressed in the days when tuberculosis was sought and found everywhere, but was probably based on misdiagnosis of patients with Graves' disease as tuberculous.

Toxic factors act by determining an abnormal compensatory reaction of the whole thyroid system. The role of iodine is definitely demonstrated, in my opinion. Thyroid self-medication for obesity also causes Graves' disease.

Traumatic factors have been described in the etiological constellation of such patients. Selye has produced in rats a syndrome resembling hyperthyroidism by exposing them to cold, injury and spinal shock. It is probable that these factors act also by upsetting the whole thyroid system in its effort to compensate the effects of the trauma.

In rare cases the cerebro-pituitary hyperthyroidism responsible for Graves' disease is caused by a tumour pressing on the hypothalamus. In other cases Graves' disease is a "second disease," the first disease being another endocrinopathy—adrenal hypocortinism, hypotestosteronism, hypoœstrinism. In this case the thyroid system reacts with hyperfunction to compensate the metabolic disturbances set up by the basic endocrinopathy, and the hypersthenic reaction oversteps the mark. Graves 'disease has been described also following intense dietetic restriction for obesity independently of any ingestion of thyroid or iodine. I have seen mild cases of this nature, and probably here also the metabolic disturbances set up by starvation have deranged a labile thyroid system.

Clinic, the Complete Form.

Onset may be acute but is usually slow and progressive. The first presenting symptoms are nervousness, irritability, increased perspiration, tremor of

the hands, and sometimes palpitations and tachycardia. Less frequently it is the morphological appearance, which shows occurrence of exophthalmos and a slowly developing goitre, that first strikes the patient.

When the disease starts before the end of the period of growth an acceleration of development is noted, bearing on height, epiphyseal union and mentality.

When the disease is fully constituted it shows a rich symptomatology, which can be studied best by considering the various syndromes delineated in the introduction as belonging to constitutional diseases.

The General Syndromes. *Morphological syndrome, including goitre and ocular manifestations.* The habitus is characterised by a striking facial expression, tallness, thinness, skin pigmentation and disturbances of hair development. The facial expression in cases with exophthalmos is one of fear, imparted principally by the exophthalmos itself. In cases without exophthalmos the face expresses sadness, tragedy or even horror, mirroring the disturbed inner life. The facial traits are highly mobile. Hair is abundant on the scalp at onset but becomes grey very early and falls, both greyness and falling occurring frequently in patches. The eyebrows also are abundant and thick, meeting over the nose.

Tallness is noted in individuals attacked by the disease before the end of the period of growth, but may be found also in cases of later development as Graves' disease develops in persons of hyperthyroidean constitution, who usually are tall. Leanness may reach a high degree, despite the abundant feeding of these patients through their voracious appetite. In many cases, however, obesity limited to the legs is encountered The skin is thin and moist, and in about 15 per cent. of cases shows a melanotic pigmentation ranging from sun-tan hue to the colour of iodine-painted skin. This pigmentation usually appears in patches on the palpebral region (Jellinek's sign) and on parts exposed to the friction of clothes, such as the waist in women. The hands and feet are long and thin, another trait of hyperthyroidean constitution.

Goitre is very frequent but not constant. It varies in degree but does not, as Graves himself remarked, attain the high dimensions observed in simple goitre. On palpation it gives the impression of a smooth diffuse parenchymatous goitre, but one lobe, usually the right, is more developed. When nodules are apparent, attention is directed more to toxic adenoma. Characteristic of this goitre, however, is its vascularity, a point stressed by Graves. This is evidenced by variations in the volume of the tumour occurring even in the course of the day and often in relation to the occurrence or cessation of palpitations. It is indicated also by thrills and bruits. The palpable thrill is felt as a systolic purr in the region of the upper pole, at the upper thyroid arteries, and more rarely at the centre of the lower pole of the gland. Bruits are heard on auscultation of the goitre more frequently than thrills (in 77 per cent. of cases according to Lerman). They are usually systolic, resembling a blowing cardiac murmur. Their mechanism is probably similar to that of placental bruits.

Exophthalmos is met in 75 per cent. of cases. It is due to an

increased volume of the orbital contents or to functional disturbances of the external ocular muscles (the conception of spasm of Muller's muscle is no longer in general acceptance). It is determined not by excess of thyroid hormone but probably by an excess of thyrotropic hormone, and in fact not only does it fail to retrocede after thyroidectomy but frequently increases after the operation, or makes its appearance in patients who had not shown this symptom before their operation. It is more common in males.

Clinically it shows a wide degree of variation. In mild cases it is simply a peculiar stare, the eyes appearing brilliant. In moderate cases it is more distinct and gives the expression of terror which patients do not lose even when they laugh. In severe cases it may reach luxation of the eyeballs. When moderate, exophthalmos can be reduced. When accentuated, it may allow ocular infective complications to occur through deficient protection of the eyeballs, and these complications may be so severe as to necessitate enucleation. Exophthalmos is usually bilateral, but in about 15 per cent. of cases is unilateral. It may retrocede with the general improvement but not always in proportion to other symptoms, and may even be aggravated by thyroidectomy, as already stated, or occur after thyroidectomy in individuals hitherto free from it. It should be remembered that many women have normally bulging eyes, and I have seen such cases, showing also manifestations of nervousness, misdiagnosed as exophthalmic goitre.

The other eye symptoms which may occur in non-exophthalmic cases are numerous, according to various descriptions, but only two such signs are important enough to merit consideration. Graefe's or lid-lag sign consists in a lagging of the lid, which fails to follow the downward movement of the eyeball when the patient is directed to look downwards. It is due to spasm of the levator palpebræ superioris. Stellwag's sign is diminution or absence of blinking. Normally the eyes blink reflexly about five times per minute. In hyperthyroidism they may blink only once in two or three minutes. In many exophthalmic cases, however, irritation of the eyes causes frequent blinking.

Night blindness is sometimes encountered. It is probably due to the disturbance of liver function through thyrotoxicosis and thus to disturbance in vitamin A metabolism.

Reactivity syndrome. The particular reactivity is characterised by asthenia with motor restlessness, intolerance to heat with hyperthermic reactions, increased appetite, sensitivity to various stimuli, increased resistance to quinine, and diminished resistance to electrical currents.

Asthenia is often considerable and occurs during the day in spurts. Motor restlessness alternates, and usually dominates the picture. The patient cannot sit still but moves incessantly, getting up, sitting down again, touching and moving objects unnecessarily, running his fingers through his hair, tapping the floor with his feet, plucking at his tie, adjusting his clothes, continuously buttoning and unbuttoning. This behaviour is characteristic in the waiting-room.

Intolerance of heat is constant. Such patients cannot bear heat of any

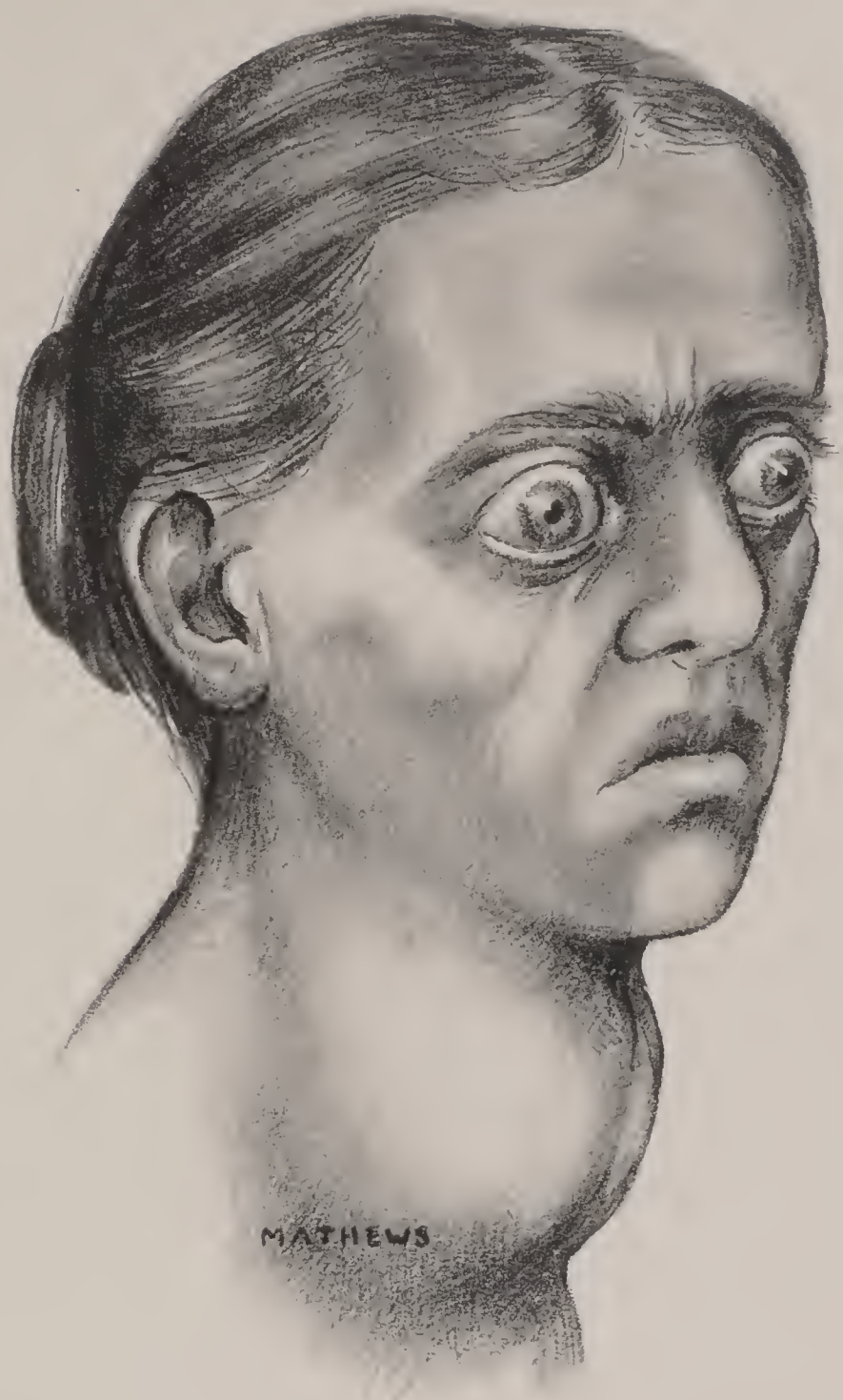


Fig. 1
GRAVE'S DISEASE. NOTE LIDLAG

kind, even in food. They dislike wearing much clothing, and at night throw off the blankets and insist on wide-open windows even in winter. Winter is their best season, and their favourite resorts are in cold climates. The skin feels hot, and usually the handshake also. Hyperthermic reactions are frequent, taking the form of chronic febricula or even fever, as I pointed out in 1920 in introducing the conception of nervous vegetative-endocrine fever. This febricula or fever is due to intensification of oxidations, and represents an exaggeration of the mechanism through which the organism raises its internal heat for protection against cold and infections—a mechanism under thyroid control.

Perspiration is increased. The slightest exertion or emotion brings drenching sweats, which may even occur spontaneously during the night. Such patients present a dripping hand to be shaken in greeting.

Hyperthyroideans are over-sensitive to all external stimuli, to shocks, jars, light and noise. When the physician approaches the bedside they jerk into an upright position and throw back the bedclothes. Such patients are very sensitive to adrenalin and scopolamine but resistant to quinine. Their appetite is often enormous.

Decreased resistance to electric currents and thus increased impedance angle complete this rich reactivity symptomatology. Brazier attempted a quantitative diagnostic evaluation of the thyroid function on the basis of the increase in the impedance angle, but as already pointed out, this attempt failed. Diagnosis can never be based on one test alone.

Mental syndrome. The Graves' psychology is characterised by active cerebration and agitation, emotivity, irritability and anxiety, depressive and cyclothymic reactions, psychosis and obstinate insomnia. This syndrome results from the intense metabolism of the cerebral cortex.

Active cerebration, the leit motiv of the mental syndrome, is shown by the great liveliness in conversation, the rapid association of ideas and the retentive memory exhibited by these patients. Their talk is fluent, rapid and continuous, and their loquacity is often such that no one else in the company has the opportunity of speaking. In the more accentuated cases this active cerebration results in agitation, although placid hyperthyroideans have been described. In general, such patients are restless, doers, never spectators. As soon as they are awake they are on the go, bustle about without fatigue all day, go to bed late and cannot bring themselves to sleep. In a more accentuated degree they never cease moving, rush up and down stairs needlessly, and are continuously disturbing and rearranging things.

Emotivity, irritability and anxiety are constant. They represent three degrees of the same disturbance of the emotional tone. Emotivity is the initial disturbance, and causes the patient to vibrate intensively to joys and sorrows, to be "highly strung." This emotivity, when exaggerated, results in irritability, and the patient becomes irascible, cannot stand contradiction, flares with anger on the slightest provocation, and thus is liable to act impulsively. Anxiety represents a higher degree of intensified emotivity.

As the hyperthyroidean feels intensely he exaggerates the dangers that beset human life, and develops anxiety for himself and for his family. Within the frame of this general anxiety phobias develop. The patient fears that his disease will have a bad outcome, he dreads loss of money or a misfortune for his dear ones. Fear gains a victory in him and is expressed in the face independently of exophthalmos.

Depressive and cyclothymic reactions appear in the clinical picture, originating also from the exaggerated emotive tone. Depression amounting to melancholia results from the intense response to the sorrows of life. It is a frequent manifestation of Graves' disease and is the cause of the tragic expression of the face independently of exophthalmos. These patients have fits of crying, often without reason. They admit that they have nothing to cry about, and are ashamed of their behaviour, but they cannot help it. Cyclothymic reactions are rarer and consist in alternation of ungrounded elation with depression and melancholia. The emotional sensitivity of hyperthyroideans sways them back and forth from exhilaration to profound sadness.

Psychosis represents a higher degree of mental involvement which occurs in predisposed individuals. Sometimes this takes the form of Bleuler's hyperthyroidean psychosis marked by extreme excitement, dissociation of thought, confused delusions, hallucinations of hearing and sight and eventually of taste and smell. At other times it takes the form of a classical manic depressive psychosis or, more rarely, schizophrenia. Psychosis is not a direct symptomatic result of hyperthyroidism but an indirect manifestation; in other words, the Graves' disease is only a contributing factor. Such individuals are potential psychotics because of various factors, mostly unknown. Before the advent of the Graves' disease they develop a manic depressive psychosis or a schizophrenia but not of such a degree as to become manifest. Hyperthyroidism, through its toxic metabolic action on the cerebral cortex, renders the psychosis patent. Just as some subjects with a diminished cardiac reserve independent of their hyperthyroidism develop cardiac decompensation following the onset of Graves' disease, other individuals with previous diminution of their mental reserve become decompensated mentally through the same toxic metabolic drive. Hertz coined the term " mental decompensation."

Obstinate insomnia is a major characteristic and an early symptom. The hyperthyroidean cannot sleep because he thinks too much. He ponders on what he has done during the day, plans what he is to do next day. He cannot relax. He tosses about in bed, sweating, with his heart throbbing. He may snatch some sleep towards morning but he wakes tired, gloomy, irritable, unfit for work.

The sexual syndrome. Disturbances of menstruation are nearly constant in hyperthyroidean women. They are usually of hypomenorrhœic type but I have seen many cases with hypermenorrhœic manifestations. Dysmenorrhœa also is noted, although less frequently than in hypothyroidism. Fertility is not impaired but pregnancy is usually disturbed. Miscarriages occur, generally in the first four months, and post-partum complications are extremely frequent.

Pregnancy aggravates all symptoms of Graves' disease, and although there are exceptions to this rule it is better to avoid pregnancy in women with distinct Graves' disease and to supervise strictly the pregnancies of women showing any evidence of hyperthyroidism even in mild form. When pregnancy has started it should not be interrupted, but the condition should be treated with care. Even thyroidectomy has been performed safely in pregnancy, but of course should be avoided whenever possible.

The Organ Syndromes. *Circulatory syndrome.* Cardiocircultory manifestations dominate the organic symptomatology in Graves' disease. The cardio-circulatory symptoms can be described in two forms, simple hyperthyroidean heart (or hyperthyroid myocardia, to use Laubry's term) and hyperthyroidean myocarditis.

Simple hyperthyroidean heart is a direct manifestation of hyperthyroidism, resulting from the metabolic disturbances engendered by this condition as well as by the direct action of thyroxin. It is a simple cardiovascular erethism which leaves the heart muscle undamaged and disappears with cure of the thyrotoxicosis. It is characterised by the tetrad tachycardia, palpitations, arrhythmia and high pulse pressure. Tachycardia, the leading symptom, ranges from slight acceleration of the pulse to 150 or more. It is unvarying in the course of day or night and follows the fluctuations of basal metabolism. It is accentuated by emotion, physical effort and digitalis, and improved by iodine. It is accompanied by dancing of the carotid arteries. Palpitations are accompanied by a sensation of pulsation in different parts of the body and I have often noted aggravation during sleep even in the absence of goitre, the patient sleeping normally but soon waking with palpitations and anxiety. Arrhythmia, mainly an auricular fibrillation or extrasystole, develops in advanced cases, but even here does not arise from heart damage, as it does in hyperthyroidean myocarditis. Together with arrhythmia or independently a passing functional dilatation of the heart may be noted, and murmurs, chiefly systolic, are heard. These also are independent of myocardial involvement, arising from changed blood hydraulics of the cavities through exhaustion of the overworked myocardium. They disappear with cure of hyperthyroidism. High pulse pressure is frequent.

Hyperthyroidean myocarditis may be an indirect manifestation of hyperthyroidism, deriving from various factors but rendered manifest or accentuated by the intense thyroxin drive. In many cases, however, it is a direct manifestation and represents the organic phase which succeeds the purely functional phase of hyperthyroidism heart disturbance, abnormal function making an abnormal organ. Its characteristic tetrad is formed of organic dilatation, organic arrhythmia, electrocardiographic changes and high blood pressure. Organic dilatation is detected clinically and radiologically, is accompanied by murmurs resembling those of an orificial lesion and often ends in congestive heart failure. Arrhythmia is most frequent in the form of auricular fibrillation or extrasystole but is more lasting than in hyperthyroidean heart. Other forms of arrhythmia, particularly heart block, also have been described but are

rarer (Asher and Borsey). Electrocardiographic changes are the rule and have been reviewed recently by Gordon. Apart from those indicating anhythmias, outstanding signs are low and notched T waves, prolongation of the PR interval and high QRS complex. There is no unanimity on this point. Recent work, mainly that of Bodansky and his co-workers, has shown the importance of disturbances of the myocardial metabolism in the occurrence of these changes. Elevation of blood pressure, frequent but not constant, completes the picture of hyperthyroidean myocarditis.

The cardiovascular erethism of Graves' disease is manifested by the visible beating of the carotids. The skin capillaries are for the most part dilated, and there is at the same time an increase of intracapillary pressure (Roberts and Griffith, 1937).

Nervous syndrome. The outstanding nervous manifestation is tremor. This is a muscular response to rhythmic disturbances of the corticocerebral motor cells which, through the intensified metabolic drive, have had their threshold of motor discharge lowered. The tremor of Graves' disease is both subjective and objective, most patients experiencing at the same time a feeling of internal trembling. It is a quiver, of fine type, eight or nine oscillations per minute, thus twice as frequent as in paralysis agitans. It is incoordinated, each finger vibrating at a different phase in contradistinction to the more synchronised tremor of alcoholism and general paresis. It is particularly, although not absolutely, localised in the hands, where it can be rendered visible by a sheet of paper placed on the extended fingers.

Muscular asthenia, myasthenia, is very frequent, and determined by the disturbance of creatine metabolism encountered in Graves' disease. In accentuated cases even special lesions of the muscles have been described by Askanazy, a diffuse process of degenerative atrophy of the muscle cells, fatty infiltration, loss of striation, degeneration of the nuclei. The myasthenia is usually manifested by intense fatigue, a very early manifestation which in doubtful cases should guide diagnosis. The patient feels weak. He experiences difficulty in going up and down stairs, walks with a waddling gait and often feels his legs giving way. In more advanced cases paroxysmal attacks of paresis or paralysis occur. Bilateral muscular atrophy, a thyrotoxic myopathy, has been described by F. B. Parsons and R. J. Twort.

Respiratory manifestations are effort dyspnœa secondary to cardiac disturbances and abnormal respiratory sensations, due probably to direct action of thyroxin on the respiratory centre. These sensations often take the form of choking provoked by any pressure on the thorax or around the neck, which is so badly tolerated that even in non-goitrous cases the pressure of collar or any other clothing cannot be supported. In other cases patients complain that they cannot fill their lungs sufficiently with air. They gasp, particularly in hot weather, heat aggravation being characteristic of hyperthyroidism. Finally, the symptom complex of suffocation during sleep is noted. Such patients sleep normally but after a short time awake gasping. They sleep again but

once more awake as if suffocated. This symptom occurs in both goitrous and non-goitrous cases.

Digestive manifestations are diarrhœa, nausea, vomiting and acute abdominal attacks. Diarrhœa is the most frequent. Stools are numerous, often as many as thirty or forty daily, occur most frequently in the morning and are watery and frothy in appearance. In severe cases vomiting complicates the picture, and combined with diarrhœa leads to ketosis terminating in coma. Nausea and vomiting may exist independently of diarrhœa and of acute abdominal attacks. These attacks are rare but diagnostically important, and may simulate appendicitis, cholecystitis or perforated peptic ulcer. As such diseases, particularly peptic ulcer, may occur in hyperthyroideans, the diagnostic picture is often very difficult to elucidate.

Locomotor disturbances consist in osteoporosis, fibrositis and arthritis. Osteoporosis is detected radiologically and arises from the intense calcium and phosphorus metabolism determined by excess of thyroxin. Fibrositis and arthritis are frequent, hyperthyroideans complaining nearly constantly of pain in fasciæ and joints. The constitutionally minded clinician can detect hyperthyroidism in many cases of chronic " rheumatism."

Urinary disturbances consist in pollakiuria and polyuria. They are rare and are attributed to irritation of the nervous control of the kidneys.

Apart from the fall of nails and alopecia areata already described, other *skin manifestations* occur. They are due to the intense metabolic drive involving skin and phaneres. The skin is nearly always thin and moist, but œdema of myxœdematous type is sometimes seen. The most frequent type is pretibial myxœdema. A hard œdema is localised on that region, and biopsy shows pressure from excess of mucin. It occurs frequently, but not always, after thyroidectomy but is not influenced by thyroid treatment. There are other types of skin myxœdema, of less obvious association with hyperthyroidism. An instance is the atypical myxœdema of Jadassohn-Doesseker, in which lesions are circumscribed or disseminated, tuberous or plaque-like, lichenoid, papular, fibromatoid.

Biochemical Syndrome. The following are the outstanding items in this important syndrome.

1. Increase in basal metabolism. Mild cases show an excess of 16–20 per cent., moderately severe cases an excess of 20–40 per cent., and severe cases are more than 40 per cent. in excess. It is an essential diagnostic feature and fairly parallel with the severity of the disease. The technique needs great care, and it should be remembered that psychological factors, emotions and fears, act on the basal metabolism and can lead to errors of interpretation. Other diseases showing an increased basal metabolism are leukæmia, fever and polycythæmia.

2. Diminution of creatinine in the urine and presence of creatine. Creatinuria is an important feature, and may run parallel with the gravity of the disease.

3. Decrease of cholesterol in the blood. This is another important feature

running parallel with the severity of the disease and the effects of treatment. Technique is delicate, and normal standards vary from 110 to 290 mg. in adults.

4. Increase of iodine in blood and urine.

5. Evidence of increased protein catabolism, negative nitrogen balance, excess of nitrogenous products in the urine, increase of neutral sulphur in the urine (indicating intensification of endogenous metabolism), diminution of the serum protein level in the blood.

6. In some cases hyperglycæmia and glycosuria, in others only alimentary glycosuria and a more or less diabetic curve of the glucose tolerance test.

7. Evidence of easy loss of water, shown by Volhard's test, but water retention occurs in some cases.

8. Excessive calcium in the urine.

Thyrotropin has been found decreased in the urine. This does not indicate a decrease of thyrotropin secretion from the antepituitary, but according to experimental work indicates that the thyroid gland fixes or neutralises more thyrotropin than normally (Rawson, Sterne and Aub).

Of all these findings the first four have the most diagnostic importance.

General Course of the Disease. Graves' disease begins progressively, develops as a slow subacute condition but is interrupted by acute exacerbations, thyroid storms. These occur usually after operation but are seen also in non-operated cases, where they occur either without apparent cause or after an intercurrent illness, a physical or mental trauma. They represent a fulminating thyrotoxicosis of obscure mechanism. Some authors hold that they are due to severe hepatic insufficiency. In point of fact glucose, which protects the liver, has good effects in such attacks, and is used preventively after operation. Further, at autopsy of such cases a high incidence of degenerative changes of the liver has been found (Beaver and Pemberton). Seventy per cent. of goitre deaths at Ann Arbor, as reported by Maddock, were due to thyroid crisis, one-half occurring before operation. According to Waldenstrom such thyroid storms are thyroid encephalopathies and even encephalo-myopathies.

Symptoms are restlessness, irritability, delirium, psychotic disorientation, a pulse rate of 200 and hyperpyrexia, which is not due to infection but like sunstroke reflects the toxic destruction of the body's organisation for eliminating heat. Myasthenia is intense. Repeated vomiting and diarrhœa are described in Bansi's case. Perspiration ceases. A diffuse redness invades the teguments. Collapse and coma set in rapidly. Death occurs in three-quarters of cases.

Relief and cure are brought about by high doses of iodine and glucose.

Untreated and inadequately treated cases of Graves' disease may last from two to four years and recover. More acute and more chronic cases, however, are seen. Medically treated cases show a higher percentage of recoveries (41 per cent. according to Campbell) and a shorter duration of the disease. For surgically treated cases there is no concensus of opinion. Campbell and some other authors regard the proportion of recoveries as equal to that of

medically treated cases, others consider it much higher, and Clute and Veal give the figure of recoveries as 95 per cent., which seems exaggerated. There is no doubt, however, that *severe* cases of Graves' disease treated surgically show a greater proportion of recoveries than equally severe cases treated medically. Statistics give no solution to the problem, as individual variations are too numerous.

Patients with Graves' disease who do not recover may enter into a chronic state of hyperthyroidism, into a state of hypothyroidism, or more frequently into a mixed condition of hyper- and hypothyroidism, develop psychoses (a rare eventuality) or die. Death occurs from cardiac complications or in the course of a thyroid storm.

Clinic, Special Forms.

The ophthalmic form, which has recently been well studied (Means) is characterised by the predominance of exophthalmos and eye symptoms in general. The general symptoms of hyperthyroidism are not very accentuated, and even when the ophthalmic form occurs after thyroidectomy hypothyroidism may exist. Physiopathologically it represents hyperfunction of pituitary thyrotropin or of another pituitary hormone not yet determined. Such cases should not undergo thyroidectomy if possible, and Means prefers pituitary radiotherapy. Exophthalmos can progress so much (malignant exophthalmos) that decompressive operations such as Naffziger's operation will be needed.

Formes frustes are extremely frequent, and every internist should be watchful for such conditions. Predominant symptoms are nervous and physical irritability, intense activity, some tachycardia, easy perspiration. The raised basal metabolism gives the thyroid stamp to such conditions, usually diagnosed as psychoneuroses.

Oligosymptomatic forms also are very frequent. They are characterised by the dominant position in the clinical picture of one of the many syndromes of Graves' disease. This is usually an organ syndrome, and the clinical picture is that of a particular disease such as rheumatism, cardiopathy, neurasthenia, chronic diarrhœa, alopecia areata. The basal metabolism is increased and iodine has good effects.

Associated forms have been described, but this point shows great confusion. For instance, there is not a true association of Graves' disease and acromegaly. The disease here is an eosinophile adenoma causing hypersecretion of growth hormone as well as of thyrotropin. The most interesting associated form is that combining hyperthyroidism with hypothyroidean manifestations. It is relatively rare and is encountered in some post-operative cases.

Graves' disease in children. It is very rare. Bram finds 2·5 per cent. of cases of Graves' disease under 12 years of age. Etiologically focal infections of teeth and tonsils play a preponderant part, psychic trauma being far less important. Clinically the complete picture can be seen. Exophthalmos and circulatory disturbances are marked. There are also some special signs such as unusual augmentation of height and enuresis (in 31 per cent. of cases, according to

Bram). Weakness of the quadruceps is another sign, which can be tested by making the child step on to a chair. Operation is less dangerous in children than in adults, as in children the myocardium is healthier and more resistant.

Diagnostic Leaders.

Typical cases with goitre or exophthalmos or both offer no difficulty in differentiation from other diseases. Cases without either manifestation are more difficult to diagnose, particularly in their differentiation from Parkinsonism, tuberculosis and neurocirculatory asthenia. Parkinsonism can prove misleading through the tremor and emotionality, but the tremor is slower, the oscillatory movement uniform with longer excursions. Other concomitant signs of Parkinsonism, as well as the state of the basal metabolism, offer help, but it should not be forgotten that Graves' disease can coincide with Parkinsonism, the diencephalic lesion in Parkinsonism extending to the thyroid hypothalamic centre or its cortical connections. Tuberculosis has been and is an important pitfall, as it shows tachycardia, nervousness, febricula, digestive disturbances. A thorough clinical and radiological exploration precludes this error. Further, in tuberculosis basal metabolism is normal except when fever occurs. Neurocirculatory asthenia shows circulatory disturbances akin to those of Graves' disease but usually more distinct during effort. The other symptoms of Graves' disease do not exist and the basal metabolism is normal.

Parry-Graves disease should be differentiated from toxic thyroid adenoma (see Chapter X) and from the hyperthyroidisms symptomatic of a primary pituitary condition such as those found in acromegaly and gigantism. These are incorrectly described as "association of Graves' disease with acromegaly (or gigantism)." Diagnosis of mild and incomplete forms is probably the most important problem. These forms are often misdiagnosed as "neurasthenia," "fibrositis," "nervous heart," and so on. Knowledge of the "generals" and biochemicals of Graves' disease and endocrinological thinking help in the avoidance of these pitfalls. One must be very careful not to become a "gland fanatic," but on the other hand very many cases of Graves' disease are diagnosed only later, when treatment is less effective. It should be remembered that the mild and atypical forms outnumber by far the typical cases.

Internistic Treatment.

This is the basic treatment in Graves' disease. It is absolutely indicated in all mild cases and those of medium severity, as well as inoperable severe cases. It is used in conjunction with surgery in severe cases, and in those cases of moderate severity in which special conditions preclude a long exclusively internistic treatment but demand a short cut. Surgery relieves hyperthyroidism by removing part of the hypersecreting thyroid. It does not, however, remove the basic condition, which is hyperfunction of the whole thyroid system. This does not mean that we should not consider surgery in Graves' disease, but undoubtedly the indications and the results of surgical treatment of this disease have been exaggerated. Surgical statistics have

erred on the side of over-optimism because they have included under the term thyrotoxicosis not only true Graves' disease, in which surgery is only relatively indicated and partially effective, but also toxic adenoma, in which surgery is absolutely indicated and definitely effective. Furthermore, many patients operated on for Graves' disease have not returned to the surgeon but seek relief elsewhere, yet continue to figure as "successes" in surgical statistics. Finally, it is probable, as the surgeon Liek has pointed out, that many so-called surgical cures are due to the lengthy pre-operative treatment in the nursing-home, to careful post-operative care and to the psychological effects of the operation.

The following internistic procedures have proved effective and should be used in combination according to individual indications. Cure can be effected in most cases with this treatment provided it is prolonged for five or six months.

Psychotherapy. This is a major procedure, and its importance is apparent when the great part played in the disease by mental factors and chiefly by the cortico-diencephalic connections is considered. Ample clinical observations testify to its efficacy, and Liek's view, already quoted, is even that many surgical interventions act through their psychotherapeutic component. In most cases the usual psychotherapy of the internist, consisting in inspiring confidence and allaying fear, is sufficient. Much depends on the psychological insight and personality of the internist, and it is a pity that students are taught how to give injections and to open abscesses but not how to allay fear. This psychotherapy must be combined with organic treatment, for hyperthyroideans are extremely critical and have no belief in mere word treatment.

In some cases the deeper psychotherapeutic methods of the psycho-analyst are indicated, and brilliant observations have proved their efficacy. A. Mahl cites the case of a woman sufferer from Graves' disease sent to him by a surgeon with the request that he rid her of some of her fears as a necessary prelude to operation, her pulse being so rapid that surgery could not be considered. After three months of treatment the psychiatrist sent her back to the surgeon minus her fears but also minus her Graves' disease. In one of Moos' patients with the same disease psycho-analysis discovered in her the existence of fear that she was pregnant. When this fear was proved to her to be groundless she improved rapidly and was discharged practically cured, the only remaining symptom being a slight enlargement of the thyroid.

Dietotherapy and Physical Methods. The diet should be high in carbohydrates and fats, low in proteins and adequate in vitamins. A high carbohydrate intake is necessary for caloric maintenance and principally for protection of the liver, so frequently involved in Graves' disease. A high fat intake is necessary not only for caloric maintenance but also, as Hoffmann and Loumos have shown, because fat increases the resistance of the body to thyroxin. Protein restriction is indicated because proteins raise metabolism and tire the liver. Of particular foods, spinach, kidneys and cress must be avoided

because of their iodine content (500 and about 400 γ per cent. respectively). Other foods contain less than 50 per cent. Among vitamins, A and B_1 are of chief importance, vitamin A because of its anti-thyroxin effect, vitamin B, because hyperthyroideans use up this vitamin and thus need it. Parenteral administration is often necessary.

Much can be done in Graves' disease by a careful dietotherapy. Samuel Soskin and Minsky have reported lately, with some astonishment, the case of a patient with severe Graves' disease who refused operation and was cured by dietotherapy alone in the form of a high fat diet.

Of physical methods the best are rest, tepid douches and high altitude climates. Absolute rest in bed is essential during acute phases. In the habitual condition prolonged stay in bed in the morning and early retiring should be advised. Tepid douches as practised in certain hydros are helpful. The physical method that has given me the best results is a high altitude cure, particularly in the Engadine. I have seen good results also from an old method applied by Delherme in my Paris days, galvanisation or galvano-faradisation of the thyroid. Radiological treatment is quasi-surgical, and will be discussed in its appropriate place.

Pharmacotherapy. *Thiouracil.* The first medicine to be considered, even in cases of pre-operative treatment, is thiouracil. Its use is based on the pioneer work of the Mackenzies and McCollum and on its first clinical application by Astwood. It acts by inhibiting thyroxin formation. It causes secondarily a thyrotropin hypersecretion which gives rise to goitre in animals, but with the small dosage such an eventuality does not occur in man. It determines a sort of medicamentous thyroidectomy. After a low dosage of 0·10–0·20 for one day, for instance, to test the tolerance, 0·20 is given twice or thrice daily. Subsequent administration must follow strictly the empirical method. Definite improvement occurs in two weeks, and after this the dosage, checked by the basal metabolic rate, is diminished progressively until a maintenance dosage of 0·20, 0·10 or 0·05 daily is reached and continued for weeks. Relapses may occur after the interruption of treatment, but another mild course corrects them. This medicine gives rise to toxic reactions, fever, cutaneous eruptions, jaundice and principally granulocytopenia and fatal agranulocytosis. Thus besides clinical supervision frequent blood counts are necessary, and thiouracil cannot be an ambulatory treatment like iodine. It is not very suitable for pre-operative treatment because it renders the thyroid friable and very vascular and thus causes difficulties for the surgeon.

Iodine preparations. Choice lies between diiodotyrosine (in my opinion the best) the B.P. liquor iodi simplex or the similar U.S.P. preparation, Lugol's solution, and the iodum 3x dilution of the homœopathic materia medica.

When diiodotyrosine is used, 2 or 3 tablets of 0·10 (diiodotyrosine Roche) are taken daily for one month, and after an interval of one month, 1 or 2 tablets per diem for another month. It is an excellent medicine, particularly in combination with digitalis, for the cardiac manifestations of Graves' disease. Liquor iodi simplex B.P. or Lugol's solution is prescribed in doses of x–xx

drops per diem for three weeks, and then again after an interval of one month for three weeks. Higher doses are not only unnecessary but also noxious, for the daily iodine requirement of man is 0·0016 whereas xv drops of liquor iodi simplex contains 0·10 of iodine. Another disadvantage of stronger doses of iodine or of a more prolonged administration is that the organism can accustom itself to this medicine, which will therefore fail if by any chance an operation is decided upon and a more drastic iodotherapy is indicated before the operation. The iodum 3x of the homœopathic materia medica has given me excellent results. Quantitatively 20 drops of this dilution correspond to the daily requirement of man, but it should be remembered that in homœopathic preparations the active element is in a special physical condition. Twenty drops daily are sufficient, and treatment can be more prolonged but always with intervals of rest.

Endocrine preparations and miscellaneous medicines. This group includes medicines useful in combination or alternation with the preceding agents. Among organotherapeutic preparations probably the best are certain pancreatic extracts of the Angioxyl type embodying the vagotonic secretion of the pancreas. They are given in courses of 12–14 injections with intervals of rest. Oestrogens are beneficial to women, probably through inhibition of the antepituitary. Dosage, to be followed by the clinical empirical method, is 10–15 mg. parenterally in the first half of the menstrual cycle, beginning with even smaller doses. Testosterone propionate has similar good effects on men and seems even more active. It is effective also for some women. The dosage is 10–20 mg. weekly. Cortin is a good alternative method for both sexes but needs careful administration as it is not always well tolerated. Glucose-insulin administration is indicated in cases showing intense cachexia.

I have observed excellent results, particularly in women, from the homœopathic preparation of ignatia 6x, of course prescribed exactly according to the indications given in homœopathic works. Passiflora and cratægus in tincture are useful. Cratægus tincture is a very good sympathetic sedative and can be given in doses of 50–100 drops daily. Phenobarbital in doses of 1–2 grains daily is indicated in certain more difficult cases.

There is no need to dwell on the importance of digitalis preparations for circulatory disturbances. Quinine hydrobromide (0·30–0·50 per diem) is effective, particularly in fibrillating cases. Möbius antithyroidin, a serum of thyroidectomised animals, and Blum's tyronorman, a substance isolated from the blood and inhibiting thyroid function, have only a theoretical basis, and I have seen no definite results from their use.

Erasistratos wrote that to give medicines is to put into motion the fingers of God. Pharmacotherapy has been neglected, first because of the therapeutic nihilism originating in the exclusively anatomopathological considerations of our fathers, and subsequently because of the uncertainty shown by experimental study. In fact, in the delicate adjustment of the ailing human being, medicines are of great help, provided that they are considered and applied according to the clinical empirical method introduced into practice by

the great school of the Greek empiricists, who were also the first systematic clinical pharmacologists.

Internistic Pre-operative Treatment. When it has been decided that operation should be performed in a case of Graves' disease careful pre-operative internistic treatment is necessary. The application of such treatment has made for great diminution of operative mortality and greater consolidation of the results. In the United States and on the Continent this treatment is always carried out by internist and surgeon in collaboration. The need for individualisation is so great that it cannot be carried out by rule of thumb, as is possible in many other pre-operative treatments.

The methods to be used are those already described in the internistic treatment of Graves' disease, but their mode of application differs because there is an immediate object—to bring the patient into fit state for operation—and because time is limited.

The primary object is to increase the weight of the patient, diminish his emotional instability and increase muscular tone—an important element in judging operation risks. The subsidiary object is to lower the exaggerated basal metabolism.

Psychotherapeutic handling is of prime importance, and has already been described sufficiently.

Rest should be advised, but not complete rest in bed except in the presence of crisis or cardiac decompensation. Exaggerated rest in bed causes loss of muscle tone, reduces the appetite and makes the patient unnecessarily nervous.

A high caloric diet should be followed, as it is so important to raise the weight. If the patient can eat well sufficient calories can be administered, mainly in fats and carbohydrates, to produce a gain in weight. If he does not eat well the operation entails great risk.

Iodine should be used more insistently. Five minims of Lugol solution three times daily is a rough average dose. If the patient shows no decrease in metabolism on this treatment there is no cause for worry provided he gains in weight. If, however, despite this treatment the basal metabolism increases and the weight falls, the position is more serious. Some authors advocate the application of X-ray, but I have no experience of this procedure. Thiouracil also is used by some for pre-operative treatment.

Ten to fifteen days of iodine treatment combined with the other procedures generally brings about amelioration and a fall in metabolism. It is not advisable, however, to operate at once in such an eventuality. It is better to continue the other internistic procedures and cease iodine medication so as to allow the patient to benefit from it. Operation can be delayed even for weeks.

Digitalis preparations are used in cardiac decompensation. In general treatment of the circulatory disturbances is one of the most delicate points. It is not a purely cardiac but a constitutional treatment.

Before operation careful search should be made for any upper respiratory infection. A carbohydrate meal should be given 6–8 hours before operation and the patient's regular dose of iodine administered with this meal.

SURGICAL, POST-OPERATIVE AND RADIOLOGICAL TREATMENT.

The operation itself consists mainly in subtotal removal of the gland, leaving the lateral parts which contain the parathyroids. Operation in stages is more rarely indicated, and the same can be said of preliminary ligation of the thyroid artery. It is an unnecessary risk to attempt any intervention on local infective foci before thyroidectomy. Careful pre-operative measures have rendered the surgical treatment of Graves' disease fairly safe. Means gives a mortality of 2·2 per cent. (in real Graves' disease), Pemberton for the Mayo Clinic 0·5 per cent.

Immediate post-operative treatment consists in the care of complications such as tetany (to be treated as indicated in the chapter on hypoparathyroidism) and thyroid crisis, which is treated with glucose and cardiac medicines. Sudden respiratory difficulties associated with hæmorrhage and formation of clots under the strap muscles of the neck can be prevented by careful observation of the patient to prevent bleeding and by a personnel trained in passing the tube.

Later, the usual internistic treatment of Graves' disease is given. The welfare of patients will be promoted by recognition that surgery can be only a passing event, although important, in a constitutional disease. The disease persists and must continue to be treated medically.

Severe exophthalmos requires special surgical intervention, the best procedure being that of Howard Nuffziger.

Radiological treatment. Irradiation of the pituitary with the object of moderating its function is a biological internistic procedure. It is thus rational but unfortunately technique has not been developed.

Irradiation of the thyroid has the disadvantage of surgical intervention in that it affects only one factor of the disease, the local thyroid hyperfunction. It is more blind than thyroidectomy, however, and when destruction of hypersecreting thyroid tissue is indicated, less effective. It has been accused of causing adhesions and thus rendering subsequent operation difficult, but this is denied by Joll and some others. Its greatest handicap is that as dosage depends not on the röntgen meter but on the individual reactions of the patient it becomes a hit-or-miss procedure. When the possibility of radiodermatitis and even cancerisation is added it is obvious that indications for this method are at present extremely limited.

CHAPTER XI

TOXIC THYROID ADENOMA

Physiopathology and Etiology. Toxic thyroid adenoma, or more simply toxic adenoma, is a disease originating in hypersecretion of the thyroid hormone, or, according to some authors, of a modified thyroid hormone, from a thyroid adenoma, a nodular goitre.

The cardiovascular and respiratory manifestations connected with goitre were described by Rose as " Kropfherz " and attributed to mechanical pres-

sure. In 1907, Leon Bernard and Cawadias attributed this condition to an endocrine factor originating in the goitre. In a series of publications from 1913, Plummer developed this conception. We encounter in thyroid pathology a general pattern discerned in endocrine pathology. There are hyperendocrinisms with hyperplasia and hyperendocrinisms with an endocrine adenoma. The thyroid hyperendocrinism with hyperplasia is Graves' disease, the thyroid hyperendocrinism with adenoma is toxic adenoma. The two conditions are distinct physiopathologically, clinically and therapeutically.

Toxic goitre is always a nodular goitre. I have never seen a diffuse parenchymatous goitre become toxic, and whenever thyrotoxic symptoms are seen in diffuse goitres they originate in a separate nodule.

There are many obscure points in the physiopathology of toxic goitre. As in all endocrine tumours, it is not known why the neoplastic cells begin at a certain stage to secrete their specific or an abnormal hormone in some cases, while in others this secretion does not occur. Anatomically, when an atoxic nodular goitre becomes toxic certain modifications can be detected, and the histological picture approaches that of goitre in Graves' disease. In toxic thyroid adenoma also it is not known whether the secreted hormone is the normal thyroid hormone or an abnormal chemical substance.

The effects of the hypersecreting thyroid adenoma are felt nearly exclusively in the cardiovascular system. Toxic goitre is essentially a cardiotoxic goitre.

Study of the etiological constellation of such patients has not yielded important results. Two factors enter into consideration, a genogenic or acquired inferiority of the cardiovascular system, and iodine administration.

As the predominant manifestations of toxic thyroid adenoma are essentially cardiovascular, a genogenic or acquired inferiority of this system is accepted. The disease attacks the middle-aged and elderly as a rule, and unlike Graves' disease is not seen in younger individuals. Most of these patients already have a damaged heart.

Excessive iodine administration has resulted in making certain thyroid adenomas become toxic. This has been observed by Kocher, who on this basis was led erroneously to hold that iodine is in general dangerous to the thyroid, whereas, as will be seen, iodine is beneficial in Graves' disease. In nodular goitres, however, iodine can cause the toxic transformation. De Quervain upheld this view on the basis of his very great experience. The activation of puberal goitres by iodine has been observed by many. Jackson and Freeman presented eighteen cases of adenomas made toxic by the use of iodine. Marine and also McLure showed that in the years 1926 and 1927, after the prophylactic introduction of iodised salt in Michigan and Minnesota, the number of goitre operations increased in these regions.

Symptomatology. Onset is progressive. In goitrous subjects the cardiocirculatory symptoms develop progressively. They consist in slight dyspnœa of effort, some palpitations and a transient tachycardia on effort. Even with such slight symptoms, and even sometimes in the absence of symptoms, Leon

Bernard and Cawadias noted cardiac hypertrophy. This, however, is the stamp of the cardiac inferiority existing in the goitrous individual independently of his goitre, a factor of predisposition in the disease.

The cardiocirculatory symptoms increase and dominate the clinical picture. Tachycardia becomes more and more accentuated and more lasting. It is less firmly established, however, than in Graves' disease, and in contrast to events in Graves' disease, is ameliorated by sleep and digitalis. It is also less marked than in Graves' disease, and the pulse rate does not reach the figures characteristic of the latter condition. Arterial hypertension, systolic and diastolic, is common, again in contrast to Graves' disease, this being another feature of the cardiocirculatory constitution of the patient independent of his goitre, which merely intensifies this condition. Cardiac arrhythmias, particularly auricular fibrillation, are very frequent and resemble hyperthyroid myocarditis more than hyperthyroid myocardia. In other words, they are more marked, more organic, a feature also due to the special cardiocirculatory condition of the patient. Symptoms of heart insufficiency with dilatation, mostly of the right heart, occur. They improve on digitalis at onset but later become more refractory, and progress to a fatal termination. Dyspnœa of effort and attacks of paroxysmal dyspnœa are prominent on account of the circulatory disturbances.

In contrast with the predominance of cardiovascular disturbances, the symptoms met in the other disease with hyperthyroidism, Graves' disease, are absent or inconspicuous. There is never exophthalmos nor any other of the Graves' disease eye manifestations. Emaciation is not marked. Fatigability exists only in a minor degree. Tremor, dermographism, hyperhydrosis and mental disturbances are absent. Such patients are included in the " apathetic hyperthyroidism " of Lahey.

Basal metabolism is not very high, and normal figures are frequently found. Cases described as hyperthyroidism with normal basal metabolism belong to the class of toxic adenoma.

Iodine is less effective than in Graves' disease, and I believe that most iodine-resistant hyperthyroidisms are cardiotoxic goitres. There are even many cases in which iodine aggravates.

The course of toxic goitre is uniform and progressive. This contrasts with the exacerbation and remissions met in Graves' disease. Thyroidectomy is conclusive, and no relapse occurs afterwards if the adenoma has really been removed. This also contrasts with the imperfect results and relapses occurring after thyroidectomy in Graves' disease. Untreated patients die from cardiac insufficiency.

The picture is so characteristic, as I noted in my first work with Leon Bernard, that the almost daily confusion of the two conditions is astonishing. Even the term " toxic goitre " is being applied to Graves' disease, whereas in reality it denotes a condition physiopathologically, clinically and therapeutically different. This confusion has been particularly detrimental as regards judgment of therapeutic methods in hyperthyroidean conditions.

The clinical picture described is sufficiently clear to make differentiation

between toxic adenoma and Graves' disease possible. This differentiation is necessary because whereas in many cases of Graves' disease internistic treatment can be used, in cardiotoxic goitre removal of the incriminated adenoma and partial thyroidectomy are absolutely indicated except in cases where the heart is much damaged and digitalis preparations are therefore the mainstay. The greatest diagnostic difficulty is offered by the adenomas developed in ectopic thyroids. The problem is at present insoluble except in the rare cases in which the biochemical symptoms, particularly elevation of the basal metabolism, direct the diagnosis.

Therapeutics. This is exclusively surgical.

CHAPTER XII

GULL'S DISEASE

(ACQUIRED OR POST-NATAL MYXŒDEMA—ACQUIRED OR POST-NATAL HYPOTHYROIDISM)

Gull's disease, described by William Gull in 1871, consists in a special symptom complex determined by a thyroid hypofunction occurring after birth, thus in the infant, adolescent or adult.

Myxœdema, a term based on the presence of mucin in the skin of patients with Gull's disease—an inconstant feature—is synonymous and even more familiar. A distinction, however, should be drawn between "acquired" myxœdema, in which hypothyroidism occurs after birth and is the real Gull's disease, and "congenital" myxœdema, in which hypothyroidism occurs during intrauterine life and constitutes another disease, Fagge's disease.

Hypothyroidism also is loosely used as synonymous with Gull's disease and myxœdema. Here also, however, a distinction should be made between post-natal or acquired hypothyroidism, which is the real Gull's disease, and the congenital hypothyroidism which corresponds to congenital myxœdema or Fagg's disease.

When we speak of infantile, adolescent or adult myxœdema or hypothyroidism we mean two things: either a Gull's disease, *i.e.*, a disease in which hypothyroidism started in the infantile, adolescent or adult stage, or a Fagge's disease, *i.e.*, a disease in which the hypothyroidism began in intrauterine life and has been projected into the infantile, adolescent or adult stage.

The term hypothyroidism is too comprehensive, including for example the symptomatic pituitary hypothyroidism of Simmonds' disease. Designations based on physiological disturbances are always wider than those based on clinical syndromes.

Physiopathology.

The physiopathological basis of acquired myxœdema is a deficiency of the thyroid system acquired after birth. This deficiency or hyposthenic reaction of the thyroxin system may originate in the glandular centre of this system

(thyroid myxœdema) or in its diencephalic centre (cerebro-pituitary myxœdema). There exists also a pituitary hypothyroxinism originating in a disturbance of the pituitary centre of the thyroxin system, but it is excluded from Gull's disease because it constitutes part of another disease, Simmonds' disease, manifesting antepituitary lesion or disturbance.

Morphologically, in thyroid myxœdema, the thyroid shows various lesions of varying degrees. They consist in sclerosis of the interstitial thyroid tissue and desquamation of the epithelium. In advanced cases the whole thyroid parenchyma is replaced by fibrous tissue. The pituitary also shows lesions representing not as in cerebro-pituitary myxœdema a primary condition but an antepituitary reaction to the thyroid lesion. Basophiles are hyperplastic and increased and the eosinophiles slightly decreased. These lesions, described by Altschule and Cooper in patients who died after thyroidectomy, resemble those of thyroidectomised animals. They are linked with the compensatory hypersecretion of thyrotropin in these cases.

The morphological manifestations of cerebro-pituitary myxœdema are less distinct. The antepituitary basophile cells may be decreased, indicating hypofunction of thyrotropin secretion. Thyroid lesions are on the same lines as those described in thyroid myxœdema but much less accentuated.

The general imbalance of the system of constitutional regulation is shown by coincident disturbances of the gonads, which react hyper- or hyposthenically, and by hyperplasia of the thymus, described first by Pierre Marie and confirmed by the work of Zondek on thyroid-thymus antagonism.

The disturbances of the system of constitutional regulation, and in particular the thyroid hypofunction, cause extensive changes in the body chemistry which are the converse of those of Graves' disease. The rate of oxidation is decreased. Protein catabolism is retarded. The skin shows an increase of muco-protein discovered by T. Cranstoun Charles, subsequently denied but confirmed lately by F. B. Byron. Glycogenolysis, fat catabolism and water catabolism are decreased. Iodine is diminished in the blood because the thyroid stores iodine instead of using it normally for the production of thyroxin. Calcium and chloride catabolism also are diminished. Altogether there is a general stagnation of most metabolic functions.

These widespread disturbances of the body react on its various functions and organs. Growth and tissue differentiation, which depend on cellular oxidative processes, are slowed. Resistance to cold is lowered, since it is in part effected by production of internal heat due to increase of cellular exidation under the control of the thyroid. Resistance to infections is lessened because normal oxidative processes seem necessary for production of antibodies. Cerebration is retarded because of the slowing of the metabolism of the cortical cells. Circulation is slowed and digestion, particularly intestinal functions, become sluggish.

Etiology.

Thyroid Myxoedema. This is determined by a series of factors acting on a more or less genogenically deficient thyroid. The gene that makes

for an inferior thyroid arises through the usual mechanisms of gene mutation or hereditary transmission.

The environmental factors concerned are traumatic, infective, toxic and nutritional. The traumatic factors consist in thyroidectomy and in excessive X-ray application to the thyroid. The infective and toxic factors act through the mechanism of thyroiditis. The nutritive factors in glandular hypothyroidism consist in certain vitamin deficiencies, but have not been well demonstrated. Atherosclerosis is an important factor in some cases of senile myxœdema.

Cerebro-pituitary Myxoedema also is determined by an interplay of a genogenic thyroid system inferiority and various environmental factors acting on the hypothalamic centre of the thyroid system. Tumours pressing on the hypothalamus cause such a hypothyroidism. They are very rare but interesting, as demonstrating clinically a cerebro-pituitary mechanism in the genesis of hypothyroidism. Pituitary tumours act through their pressure on the hypothalamus, not by disturbing pituitary function. Infective factors are probably important also, acting not as in primary glandular forms through the mechanism of thyroiditis but through diencephalitis. The role of toxic factors is shown in the hypothyroidisms following thiocyanate intoxication. Apart from this form not much is known. The role of nutritive factors, iodine deficiency and certain avitaminoses is accepted by some but has not yet been clearly demonstrated. If they are responsible they determine hypothyroidism by provoking an abnormal compensatory reaction of this system to the metabolic disturbances they cause. Certain experiments of Mislowitzer, Nissen and Stanoyevich with iodine deficiency seem to indicate this mechanism. Cerebro-pituitary hypothyroidism is in some cases secondary to another endocrinism and its genesis in such cases is explained either through direct inhibition of the whole system by another hyperfunctioning endocrine or through an abnormal compensatory reaction to the metabolic disturbances caused by the primary endocrinism. Psychogenic factors are in my opinion very important, as they are encountered so frequently in the history of these patients and their role is clearly explained by their cortico-diencephalic connections.

Clinic, the Adult Complete Form.

In myxœdema, which begins at any stage of adult life, often towards the climacteric in women and men, onset is slow and progressive.

Asthenia and fatigue generally usher in the condition, which later shows cerebral disturbances such as lack of memory and concentration—marked symptoms in the history of such patients. The body weight increases, the teguments become infiltrated, and progressively the complete picture is established.

The General Syndromes. *The morphological syndrome.* When the disease is fully established the habitus is essentially characteristic. The general appearance is one of heaviness and increased body bulk. The facies in particular reflects the myxœdematous infiltration and the slow cerebration characteristic

of these patients. The expression shows simple benevolence in mild cases, heaviness, emptiness and stupidity in more severe forms, but differs from the masklike appearance of the Parkinsonian. The eyes are hidden under swollen eyelids, the skin is wrinkled in spite of infiltration and the forehead creased in repose—an important diagnostic sign. The lips are thick, pouting and very red, except when anæmia coincides. The tongue is large and in accentuated cases hangs out dribbling saliva. It is smooth as in pernicious anæmia but not sore. Its infiltration causes difficulties in speech, which is mumbling and often inaudible. The colour of the skin is characteristically alabaster but a slight patch of pink shows on the cheeks. The whole aspect has been described as full moon, but in fact has never the regularity of the full moon. Full moon faces are found outside myxœdema.

The teeth fall easily and are prone to caries. When hypothyroxinism is of early onset they are overcrowded and irregular. The hair is brittle, sparse and falls easily. Hair cutting is needed only at long intervals. Marginal baldness, alopecia areata or even complete baldness may occur. The outer third of the eyebrows is absent (Léopold Lévi's sign). The beard grows slowly and needs shaving only about once a week.

The whole body shows distinctive features. Its bulk is increased, the increase being due to adiposis and myxœdematous infiltration. The neck is full and thick, giving a stunted appearance. Over the clavicles cushion-like swellings, granular on palpation, are seen, constituting a supraclavicular padding. The abdomen is large and protruding. Infiltration is detected in the legs by the marks left by garters. The hands are cyanotic, cold and often moist—in contrast with the dryness of the skin. They are pawlike, with dorsal padding and short stubby fingers. The nails show white lines and develop badly, are brittle and fall easily. The feet show similar features.

The skin as a whole is very dry, rough, scaly and prone to many eruptions. Dryness is due to deficient perspiration. Roughness arises from metabolic disturbances and may extend to the external auditory meatus. Frequently fine scales are found in the stockings. Eruptions take the form of acne and eczema, and show the defective resistance of the skin, which is disturbed in its metabolism. Scleroderma has been noted. Axillary and pubic hair is brittle and sparse.

Reactivity syndrome. Asthenia and slowness of motor reactions are leading features. Such patients feel tired, usually in the morning when leaving bed. Dressing and preparing for the day is a burdensome procedure. As the day wears on the patient feels better, the improvement reaching its zenith towards noon, but exhaustion soon sets in and lasts for the rest of the day. The slowness of motor reactions of hypothyroideans contrasts with the restlessness of hyperthyroxinics. They sit still, all necessary movements are carried out draggingly, they take hours to dress, they leave their chair lingeringly and in general are economical of motor energy.

Chilliness and lack of perspiration constitute the second element of the reactivity triad. The deficient oxidations make for imperfect production of

internal heat. Hypothyroideans wear much clothing even in warm weather, complain bitterly when the thermometer falls slightly, and want to stay at home by the fire. Cold aggravates their symptoms, winter being the worst season for their condition. Their central temperature is 98° or less. The deficiency of perspiration makes for dryness of the skin. Even with violent exercise these patients do not perspire.

Lack of resistance to infections is marked for colds. Many individuals, especially children who seem never free from colds and whom tonsillectomy has failed to benefit, are cured by thyroid. Acute infections, principally typhoid fever, develop very severely in such patients. Thyroxin regulates the production of antibodies from the reticulo-endothelial system. Hypothyroideans are also less resistant to certain toxics (morphia, atropine, quinine) hence care is necessary in the administration of such drugs. They are sensitive to insulin because they lack a normal anti-insulin factor, a function of thyroxin. On the other hand, they are resistant to pilocarpine and adrenalin because these drugs act on the vegetative system which in these individuals is in a state of low reactivity.

Appetite and thirst are poor. Resistance to electrical current is pronounced, as shown by Vigouroux. A corollary of this is decrease of the electrical capacity of the body and thus decrease of the impedance angle. Brazier has used this sign for purposes of precise quantitative diagnosis of hypothyroidism, but his results have not been confirmed.

Sexual syndrome. In women disturbances of menstrual flow are very frequent, although I have noted hypomenorrhœa as well as the hypermenorrhœa accepted by Gardiner Hill. Dysmenorrhœa is the most frequent menstrual disturbance. It has been explained by the antagonism between thyroxine and pitressin on the uterine movements, the lack of thyroxine allowing the pitressin to act unchecked and thus to cause intense contractions of the uterus resulting in pain.

Abortions and still births are frequent. The embryo of the hypothyroidean woman is below par, fails to develop properly, dies, and abortion occurs. The abortion is of the missed variety, the ovum being retained in the uterus for a considerable time after its death. Hypothyroidean women who have had abortions experience normal pregnancies if treated but abortion occurs if the treatment is interrupted.

Infertility also is very common. In Lintzenberg's and Carey's statistics 45 per cent. of their hypothyroidean women, who had not severe manifestations of myxœdema, were infertile. Thus hypothyroidism should always be considered in female infertility, for women who have hitherto received all kinds of treatment for their infertility become fertile when put on thyroid.

In men, sexual disturbances are less marked, but impotence and infertility have been noted.

Mental syndrome. As in all endocrine diseases, the mental symptoms are of great importance in hypothyroidism and offer probably the most valuable clues to guide treatment. They result from the metabolic disturbance of the

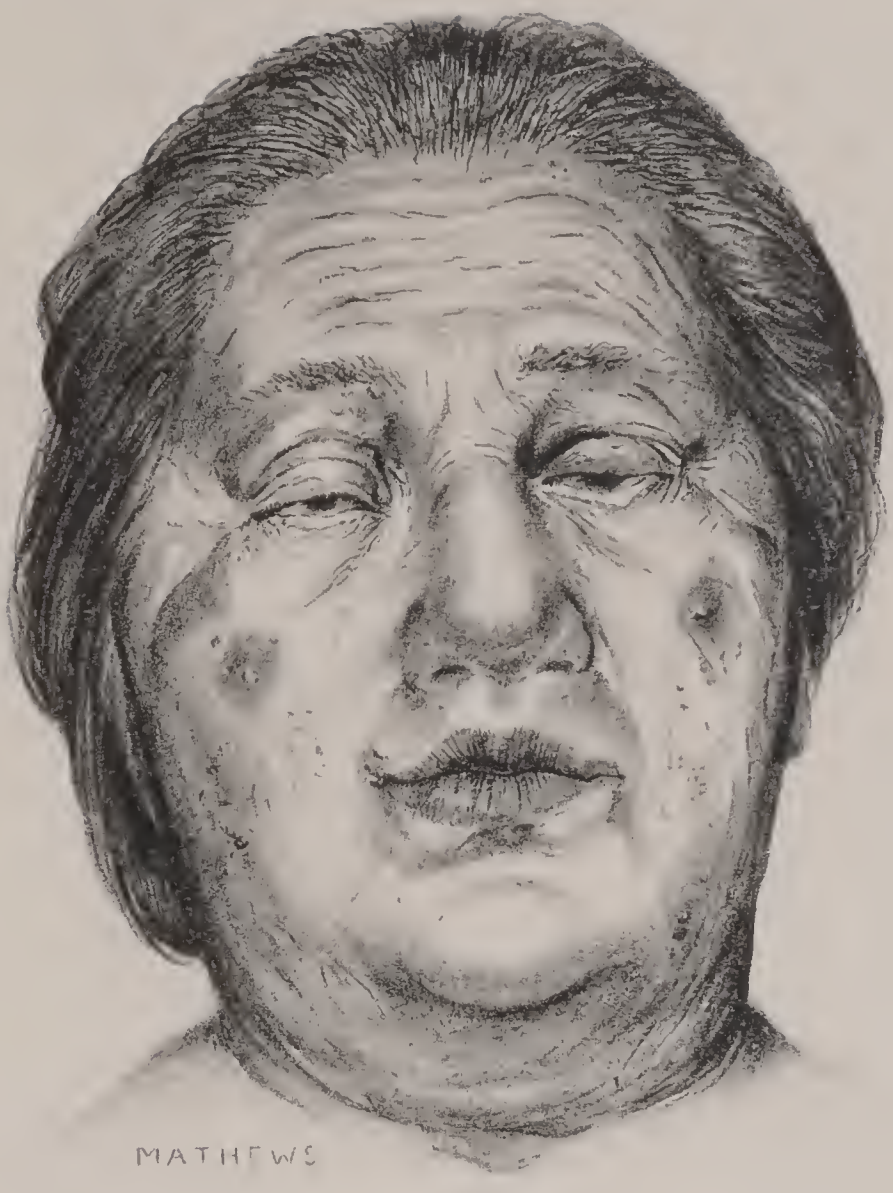


Fig. 2
GULL'S DISEASE IN AN ADULT

cerebral cortex and from purely psychogenic factors connected with the attitude of the patient towards his disease.

Slowness of cerebration is the leading characteristic. In mild cases it shows merely as laziness of thought, lack of concentration, inability to make mental effort, and principally forgetfulness, as the thyroid seems to regulate the memory in particular. These symptoms often direct diagnosis to hypothyroidism, and the number is legion of " dunces " who have risen near the top of the class through treatment of their basic hypothyroidism, and of adults whose incapacity in business has been cured by the same means. In more severe cases mental retardation ranges from mental debility to imbecility and idiocy, even to complete breakdown and dementia. Severe senile dementia of purely thyroid origin is exceptional, but as cure of the basic hypothyroidism has led to some dramatic recoveries this possibility should be borne in mind. Mental debility is more frequent in young hypothyroideans, dementia occurring more often after forty.

Apathy and indifference to the surroundings set the emotional tone, but mental exaltation is encountered, although rarely, and should be noted, for usually physicians do not associate hypothyroidism with excitability. Children may show fits of bad temper, impulsive actions and destructiveness. Adults have emotional instability and nervousness akin to those of Graves' disease, although less severe and produced by a different mechanism. In hyperthyroidism, mental excitability is explained by the accelerated metabolism of the central nervous system. In hypothyroidism the mechanism of production is an irritable weakness. In states of fatigue the individual responds intensely to any stimulus, and the metabolically deficient cerebral cortex of the hypothyroidean reacts violently for the same reason.

In severe cases psychoses occur. The usual tendency is towards depressive psychoses, although mild excitement has sometimes been observed. Individual variations depend upon the severity of thyroid deficiency and on the underlying characteristics of the patient.

Sleep is not normal. Daytime drowsiness is frequent, varying from mere somnolence to spells of sleep from which it is impossible to arouse the patient and which sometimes give the impression of narcolepsy. At night sleep is heavy, deep and dreamless.

The speech is deliberate. The hypothyroidean takes a long time to answer and likes responding with monosyllables. The voice is husky and low-pitched, the words are badly articulated, often stumbled over and slurred much as by a drunken man. Awkwardness of speech is due to cortical retardation, but also to enlargement of the tongue and thickness of the lips.

The Organ Syndromes. The organ manifestations of hypothyroidism are numerous and extremely varied. For descriptive purposes they are studied in their entirety here, but of course do not co-exist in the same patient.

Clinical practice presents hypothyroideans with well marked general symptoms and a few outstanding organ symptoms, or with symptoms predominating in one organic system and less marked general symptoms.

These organic or oligosymptomatic forms of hypothyroidism are very important, and their diagnosis allows of brilliant therapeutic results. To help diagnosis, however, the description of all the repercussions that thyroid insufficiency can have on the various organic systems is necessary. There are two varieties of organ manifestations, those like cephalalgia, bradycardia, constipation, which are frequent, of a general nature and forming part of the general picture of hypothyroidism, and those such as certain dermatoses, myodystrophies and osteoarthropathies which dominate the clinical picture over the generals, are of more local nature and rarer. These constitute the important oligosymptomatic organic forms of hypothyroidism.

The nervous symptomatology is very rich. Cephalalgia is frequent. It occurs mostly in the morning and is diffuse " en casque." It is often taken for neurasthenic cephalalgia. Motor weakness is often so pronounced that the patient can hardly walk or stand. It is frequently due to lesions of the corpus striatum, described by Mott, determined by the lack of thyroxin. Disturbances of vision range from simple asthenopia, which resists correction with glasses, to more severe derangements. Through the coincidence of œdema such derangements have sometimes been erroneously ascribed to renal causes but corrected when their hypothyroidean nature was detected and appropriate treatment instituted. Myotonia and muscular hypertrophy have been described. They usually dominate the picture and constitute an oligosymptomatic form of hypothyroidism.

The cardiocirculatory syndrome is as important as in Graves' disease, although this is not usually recognised. Simple myxœdema heart is characterised by the triad bradycardia, dilatation and hypotension. Bradycardia is the constant feature. Dilatation is seen on radiological examination, the organ appearing dilated with a clear outline and flabby " like a Rugby football." Hypotension is the least constant feature. Electrocardiography shows diminution of P waves, low or inverted T waves and low potential of the QR.S. Notwithstanding the intense dilatation there are no symptoms of cardiac insufficiency. The mechanism of production of simple myxœdema heart is imperfectly understood. Bradycardia is attributed to slow metabolism, dilatation to myxœdematous infiltration of the heart.

In more advanced cases a real myxœdema myocarditis is encountered. It is a common myocarditis involving particularly the coronary and other arteries. It is determined by the disturbances in cholesterol metabolism, a frequent metabolic feature of hypothyroidism, but also by other extra-thyroidean factors. Myxœdematous myocarditis may produce manifestations of congestive heart failure and angina pectoris, but in general is latent as the heart works at a low level because of the low metabolism. When, however, thyroid treatment raises the metabolic rate the insufficient heart is forced to work more and severe anginal attacks may occur, as observed by Ohler and Abramson, Abrami and Brule. Thus, in myxœdema the heart needs minutious examination and thyroid treatment of elderly subjects must be instituted with great caution. It is in myxœdematous myocarditis that high blood pressure is found.

The digestive syndrome offers a cardinal symptom of hypothyroidism, constipation, a symptom nearly as constant as bradycardia, mental retardation and diminution of basal metabolism. It is very marked, of the atonic type, resists laxatives but is relieved by thyroid. There are also many other digestive manifestations, taking the form of a simple atonic dyspepsia, chronic cholecystitis, chronic appendicitis, peptic ulcer, chronic colitis. In fact, hypothyroidism may be the origin of many " digestive diseases," as the digestive manifestations may constitute an oligosymptomatic form of hypothyroidism. Thus in the differential diagnosis of various digestive disorders hypothyroidism should be considered and the patient investigated from that point of view. Cases are frequent in which thyroid administration has effected a rapid cure after complicated gastroenterological treatment and even operation had failed.

Anæmia is encountered in one-half of the cases, and is usually characterised by diminution of red blood corpuscles and hæmoglobin, and by mononucleosis. It retrocedes with thyroid and iron but not with iron alone. In some cases hyperchromic anæmia of Addisonian type is seen, and here liver treatment is ineffective without thyroid. Thus hypothyroidism should be considered in cases of pernicious anæmia resisting liver treatment.

The skin with its essentially disturbed metabolism also shows many abnormalities such as various dermatoses, eczema, scleroderma, ulcers and disturbances of nails and hair. Scleroderma takes the form of scleroderma circumscripta, sometimes called myxœdematous plaques (Dubreuilh, C. S. Wright). Torpid ulcers are often of hypothyroidean origin, and Kilbourn cites a case of an enormous ulcer of the right leg, of seventeen years' duration, which disappeared with intensive thyroid medication.

The Biochemical Syndrome. Laboratory investigation reveals the metabolic disturbances indicated in the study of the physiopathology of this condition. The clinically outstanding features are diminution of basal metabolism and increase of cholesterol in the blood. The decrease in basal metabolism is diagnostic only up to a certain point, because the emotional tone influences the rise and fall of basal metabolism, as shown in many recent observations (Dunbar). Thus the basal metabolic rate may represent the emotional state of the patient as much as his thyroid function. Even this so-called specific sign of hypothyroidism, therefore, is not truly specific. Its significance is related to the whole clinical picture of the patient, and for that reason Engelbach's " rational procedure " for regulation of therapy based on basal metabolic determination is in fact, in the light of modern research, very irrational.

The increase of blood cholesterol, which testifies to disturbance of lipoid metabolism, has the same diagnostic significance, when viewed in the light of the whole clinical picture, as the basal metabolism. It is less liable to intense changes from emotional causes, however, and is more easily estimated in children. As the normal blood cholesterol figures vary between 150 and 300 mg. per cent., only figures higher than the latter are of diagnostic significance.

Creatinuria is decreased in children. Its increase, according to Wilkins and Fleishman, is a more important criterion of the progress of treatment than the basal metabolism.

Diminution of iodine in the blood is important physipathologically but has not yet reached the clinical stage. Hypoglycæmia and alimentary glycosuria are interesting within the frame of the general description but of course not diagnostic. Volhard's test indicates retention of salt and water.

The hormonal syndrome is not clear. At present the only work done has centred on the thyrotropic hormone of the anterior pituitary. Aron finds this hormone increased in the urine. This does not mean increased secretion but inability of the thyroid to fix thyrotropin, and is thus a symptom of deficient thyroid function (Rawson, Sterne and Aub). Discrepancies probably arise from the varying origin of hypothyroidisms.

Course of the Disease. A few mild hypothyroidisms may retrocede completely, usually after treatment. In general, however, hypothyroidism, both primary and cerebropituitary, is an essentially chronic disease but under perfect therapeutic control. Untreated cases end in death through cachexia and thyroid coma, very rare nowadays. Treated cases are under complete control, but if treatment starts after permanent damage has been done to the nervous system results are less brilliant.

Special Forms.

Infantile Post-Natal Myxœdema. Gull's disease or myxœdema occurring early in life shows certain special features referring to disturbances in growth and development under the influence of the deficiency of tissue differentiation by the thyroid. Thus growth lags, the body acquires a heavy undifferentiated aspect and, principally, there is great mental retardation. There are visual disturbances, digestive disturbances and disturbances of gait. Infiltration of the skin and obesity are rarer than in the adult form, and nervous excitement is often noted. The clinical picture depends on the intensity of the hypothyroidism and the age at which onset occurred. Both glandular and cerebropituitary physiopathological mechanisms are encountered, and the disease may be accentuated and complete or a mild forme fruste. The latter event is very frequent.

A regrettable confusion has arisen between infantile myxœdema and congenital myxœdema. The term " infantile myxœdema " should be limited to acquired or post-natal hypothyroidism occurring in infancy. " Congenital myxœdema " denotes hypothyroidism of congenital origin and can be seen in infants as well as projected into adult life. The difference in the clinical picture and in prognosis demands this precise distinction.

Formes frustes. These, being very frequent, are much more important than the complete form, which is very rare. As for many other constitutional diseases, the complete form has been described mainly for clarification of the formes frustes, in which symptoms are less numerous and milder. Curiously enough, the formes frustes were discovered only in 1904 by Hertoghe of

Anvers, whose work was developed in Paris by Léopold Lévi and Henri de Rothschild. Predominant symptoms are laziness of thought, bad memory, insomnia, nervousness, tendency to put on weight, constipation and dental caries. A low basal metabolism gives the hypothyroidean stamp to the syndrome. This form is often misdiagnosed as "mental breakdown" or "neurasthenia."

Hypothyroidism with leanness and nervousness. Predominant symptoms are leanness, tachycardia, nervousness and low basal metabolism. As tachycardia and nervousness are not often associated with hypothyroidism such cases are often misdiagnosed. These patients are relieved by small doses of thyroid, while large doses aggravate their condition. The so-called "dysthyroidism" described following thyroidectomy for Graves' disease belongs to this category, and it is unnecessary to postulate "a mixture of hyper- and hypothroidism."

Oligosymptomatic forms. In these one of the syndromes constituting hypothyroidism—or even part of a syndrome—dominates the clinical picture and thus gives the impression of a special disease. The generals and biochemicals of hypothyroidism, however, allow of accurate diagnosis and thus effective treatment. According to the predominating symptoms hypothyroidean obesity (rare), hypothyroidean chronic rheumatism (frequent), hypothyroidean constipation, hypothyroidean cardiopathy, hypothyroidean psychoneurosis (Léopold Lévi), have been described. The existence of these forms indicates that in all cases of obesity, rheumatism, constipation, hypomenorrhœa, menorrhagia, dysmenorrhœa, psychoneurosis and cardiopathy hypothyroidism must be considered.

Legge-Perthes' disease also may be an oligosymptomatic form of hypothyroidism. Albright has published an interesting observation on this point. Myotonia and a syndrome of generalised muscular hypertrophy are, in some cases, also oligosymptomatic forms of hypothyroidism. Such conditions accompanied by the general symptoms of hypothyroidism and showing improvement after thyroid medication have been described recently, the syndrome of hypothyroidean generalised muscular hypertrophy being seen principally in children (Debre, Semelaigne, Mollaret and Sigwald).

Diagnostic Leaders.

The accentuated form of myxœdema may offer certain difficulties in its differentiation from chronic nephritis, Addisonian anæmia and cardiac insufficiency. Chronic nephritis has in common with myxœdema puffiness of the eyelids, sallow complexion, somnolence, disorientation and visual disturbances, but albuminuria is more intense, there is no obesity or supraclavicular padding, and the basal metabolism is not low. Pernicious anæmia has in common with myxœdema fatness, heaviness and a skin colour that may approach the alabaster hue of myxœdema, but the distinctive blood picture and the absence of a low basal metabolism help to differentiate the two diseases. It should be remembered, however, that some pernicious anæmias are of hypothyroidean origin. Cardiac insufficiency with œdema is of more difficult differentiation from myxœdema with predominant heart manifesta-

tions. However, the features of " myxœdema heart " are very characteristic, and here also the investigation of the basal metabolism is of great diagnostic help. In doubtful cases careful trial of thyroid treatment should be made.

An important diagnostic stumbling-block is differentiation between the disease here described and Simmonds' disease with thyroid deficiency. which is a pituitary hypothyroidism. The importance lies in the fact that in Simmonds' disease, even in its mild forms, adrenal hypocortinism is an important element, and hypo-adrenal patients are often aggravated by thyroid treatment. The general clinical picture and particularly the intense manifestations of hypogonadism help to precise diagnosis.

Great difficulties arise in diagnosis of the very frequent formes frustes and oligosymptomatic forms of hypothyroidism, which in fact are often misdiagnosed to the great detriment of the patient. These difficulties will be overcome if the physician remembers hypothyroidism in the differential diagnosis of all cases of nervousness, mental retardation, menstrual disturbances, sterility, constipation, cardiopathies, scleroderma and chronic rheumatism, and to look in these diseases for the generals and biochemicals of hypothyroidism.

Therapeutics.

Thyroid organotherapy is the basic procedure. The pure hormone thyroxin is not used, as clinical observations have shown that its effects are inferior to those of the dried thyroid gland generally given by mouth.

Choice of preparation is sometimes difficult because the numerous thyroid preparations show differences of activity depending on the animal which has provided the gland, the season in which the extract is prepared and to technique of preparation. A rough comparison of the activity of the various preparations is afforded by the iodine content, and for this reason they are standardised according to the thyroxin-iodine content. B.P. thyroid is standardised to contain 0·09–0·11 per cent. of iodine of which at least 90 per cent. should be in combination as thyroxin. U.S.P. thyroid is standardised to contain 0·17–0·23 per cent. of total iodine. The various commercial preparations also differ in their thyroxin-iodine content, which should be stated on the packing to ensure accuracy in therapeutics. Because of these differences the physician should familiarise himself clinically with one or two brands of thyroid and use them only. He should be on his guard against proprietary preparations advertised as " more active " than others, for this activity is usually due simply to a higher thyroxin-iodine content.

Administration of thyroid necessitates strict adherence to the rules of the clinical empirical method. An initial dosage is chosen, generally low, perhaps 0·05 grams (roughly 1 grain). This is increased progressively, while careful watch is kept for symptoms of intolerance, tachycardia, nervousness, insomnia, rapid loss of weight, and for symptoms of cure, which embrace all the symptomatology and not the basal metabolism alone. After a few days the full therapeutic dose is reached and maintained for a certain time. When good therapeutic results have been obtained the dosage of thyroid is gradually decreased, always with careful watch for reappearance of symptoms, then a minimal maintenance

dose is reached and given for a prolonged period. Thus four phases can be distinguished in thyroid medication; the phase of progressive dosage with the object of determining tolerance and the full therapeutic dose, the phase of application of the full therapeutic dose, the phase of decreasing dosage with the object of determining the minimum maintenance dose, and a prolonged phase of application of the minimum maintenance dose.

Intervals are necessary in thyroid medication. Study of a single intravenous injection of one milligram of thyroxin and of its effects on the basal metabolic rate shows that these effects start at once and increase daily, reaching a maximum on the sixth or seventh day, maintaining that level for two or three days, and decreasing without exhaustion for twelve days and even for weeks. Thus repeated treatments lead to accumulation. These considerations are true also of thyroid extract, since it contains thyroxin.

The maximum therapeutic and minimum maintenance doses vary according to individuals. On the whole, if the trial phases are carefully directed, dosage can be smaller than if the procedure is done in haphazard fashion. The minimum maintenance dose is usually 5—10 centigrams in complete cases, but there are great variations. Léopold Lévi reports results in hypothyroidism with nervosism from one-sixteen-millionth of a gram, and mentions the case of a dramatist of 75 whose work was facilitated by 0·2 milligrams of thyroid but who experienced symptoms of excitation with 0·3 milligrams. Such small doses are particularly indicated in cerebro-pituitary hypothyroidism.

All this shows the importance of a careful observation of the totality of symptoms. It is utterly irrational to base therapy on one symptom only, the basal metabolic rate, a procedure termed " rational method " by Engelbach. In a complicated constitutional condition like hypothyroidism one symptom does not provide a sufficient base.

Thyroid administration may be a curative method in some cases. It helps the patient over a temporary deficiency of secretion. In other cases it enables the thyroid to rest, and after rest the gland resumes normal function (in such cases small doses are necessary). Usually, however, thyroid is only a method of substitution, and like all such methods, must be continued for life, like insulin. Unlike insulin, however, it need not be used continuously, and as it is active by mouth it has not the disadvantages of multiple injections of insulin.

Other medicines may be used as adjuvants. Sulphur is in my opinion the best agent. It is a powerful oxidiser, and can be used either in colloidal form, as an absorbable organic preparation, or in homœopathic form. It should be remembered that Hahnemann, who was an observer of genius, described under " sulphur type " (the type of the patient needing sulphur) the syndrome of hypothyroidism. Laxatives of mild biological type are important when constipation is not relieved by thyroid, for intestinal toxæmia should not be allowed to add its effects to those of hypothyroidism. Nervous sedatives, also of mild biological type, are good adjuvants for hypothyroideans with nervosism. Thymus should be avoided as it causes distinct aggravation (Zondek).

General constitutional methods are necessary for complete cure. Educa-

tional measures for young hypothyroideans enable them to adapt themselves more rapidly to life. A protein-rich diet is of great help. Physical methods are important because they help to stimulate metabolism and thus enhance the reactivity of tissues to thyroxine. It should not be forgotten that in hypothyroidism there is, besides defective thyroid secretion, an element of defective tissue receptivity of thyroid. Ultra-violet irradiation, cold hydrotherapy, sea climate and baths are therefore valuable, probably by increasing tissue receptivity. In endocrine diseases we must treat not only the incriminated gland but also the whole patient, because our object is the total reaction of the system of constitutional regulation.

CHAPTER XIII

FAGGE'S DISEASE

(CONGENITAL MYXŒDEMA—CONGENITAL HYPOTHYROIDISM)

This was the second "cretinoid disease" to be described (the first was cretinism) and the first of the hypothyroid cretinoidisms or hypothyroidisms discovered. It was described by Charles Hilton Fagge in 1871 as "sporadic cretinism." Fagge linked the condition with a lesion of the thyroid, on the basis of the cases described by T. B. Curling in 1850 as "cretinism" and dependent on similar thyroid lesions. These, however, were probably not true endemic cretinisms but similar to Fagge's cases, *i.e.*, real hypothyroidean cretinism.

Congenital myxœdema is determined by a hypothyroidism due to disturbance of the glandular centre of the thyroxin system, the thyroid gland itself, during intrauterine life.

The predominant etiological condition of its genesis are a genogenic inferiority of the thyroid gland, various metabolic disturbances of the mother due to nutritive, infective, toxic or even psychogenic factors reacting on the fœtus, and principally hypothyroidism of the mother. The maternal thyroid hormone stimulates tissue differentiation in the fœtus and thus differentiation of the thyroid, hence the effects of hypothyroidism on the fœtal thyroid.

The physiopathology is similar to that of adult myxœdema except that the deficiency of thyroid hormone starts very early and consequently tissue differentiation, particularly differentiation and thus development of the central nervous system, is deeply disturbed. Various degrees of hypoplasia of the thyroid and even complete aplasia are encountered, principally according to the intensity of the genetic disturbance.

CLINIC.

Developmental Syndrome. The morbid process starts during embryonic life and results in hypoplasia or even aplasia of the thyroid. This early thyroid disturbance causes grave developmental defects.

The only symptoms seen at birth are overweight and delay in the falling of the umbilical cord. These are not sufficiently characteristic, and diagnosis is possible only after the sixth month, when the slowness of development becomes apparent.

The infant does not grow according to the usual anthropometric standards. The teeth do not erupt at their normal time (6th–9th month for the central incisors, 8th–11th month for the upper incisors). Speech is retarded, and whereas a normal child of 12 months pronounces such words as "ma-ma" and "da-da" and has a vocabulary of five or six words at 18 months, the congenital hypothyroidean of 18 months utters only monosyllables, and can utter sentences only in the second or third year or even later. Walking and motor reactions also develop late, and for appreciation of this symptom it should be remembered that at the age of six months the normal child can move from back to stomach, after the ninth month it sits unsupported, after the twelfth it crawls, and at eighteen months walks about and climbs chairs. Retardation of habits of cleanliness is more difficult to appreciate because normal standards are lacking and thus only a very distinct delay is significant. Clean habits may never develop, enuresis in particular being permanent.

Retardation of mental development is the most important feature, but demands great clinical insight for its estimation. The clinician should familiarise himself from his early student days with the mental as well as physical features of growing children; only by this means will he appreciate defects in mental or physical development. The mental tests derived from the work of Binet Simon are helpful but cannot compete with the "intuitive clinical method" based on the clinical experience acquired through study of developing children. These tests give false security, and the famous intellectual quotient has not mathematical precision. I have often sent the same child to different reliable mental testers and have seen great discrepancies in the results.

The General Picture. In its general lines this resembles the picture of adult hypothyroidism, but is much more accentuated as the damage to the general development is very great.

The habitus is characterised not only by heaviness and infiltration but also by dwarfism and general deformity. Dwarfism is constant, although less marked than in many cases of pituitary dwarfism. Obesity develops towards the second year of life, involving the whole body but with emphasis on certain regions, as between the scapulæ and in the supraclavicular fossæ, where it constitutes a characteristic padding. It is the facies, however, that is the most striking element. The expression is one of apathy, stupidity, idiocy, and in accentuated cases can be likened to that of a pig. The eyelids are puffy, the palpebral fissures narrow but horizontal without the slant of the Mongol. Strabismus is frequent. The cheeks are baggy but without the circumscribed malar flush of the adult hypothyroidean. The root of the nose is depressed (saddle nose), indicating faulty growth of the sphenoid bone. The tongue is large to the point of clumsiness and sometimes protrudes from the mouth

dribbling saliva. It is red in contrast to the pallid face. Dental disturbances include delayed eruption, overcrowding, decalcification and sepsis. The overcrowding is due to development of the permanent teeth before the decidual teeth have accomplished their cycle. Thyroid treatment contributes greatly to orthodonty.

The rest of the body participates in the stuntedness and deformity. The neck is thick and full, the abdomen protrudes and is infiltrated with fat. Umbilical hernia is very frequent. The external genitals are sometimes underdeveloped but this sign is of difficult appreciation in childhood. The hands are broad and paw-like, with characteristic dorsal padding, the nails brittle. The skin is rough, dry and scaly, but has not the alabaster colour of the adult hypothyroidean. Hair develops badly. An important sign is offered by radiological exploration, indicating retardation in the occurrence of centres of ossification.

The mental syndrome also is an exaggeration of that seen in adult hypothyroideans. The mental retardation in particular is very notable and may reach the degree of mental deficiency. Defects of speech are constant. Apathy dominates the emotional tone but mental restlessness with destructiveness and irritability have been reported. These children break their toys and other objects, fight with their brothers and sisters and show bad temper, especially when they are not understood.

The reactivity manifestations are those of hypothyroidism in general. Slowness of motor reactions, chilliness and lack of perspiration, susceptibility to infections, and anorexia.

The organ repercussions are limited to the cardiocirculatory and digestive systems. Bradycardia is very frequent but other cardiac manifestations are much rarer than in Gull's disease. Anæmia of hypochromic type is equally as frequent as in the adult. The outstanding organic repercussions, however, refer to the digestive organs. Constipation is a cardinal symptom. Digestive upsets are also nearly constant, and in fact many infantile gastroenteritis regarded as infective clear up with thyroid.

Of the biochemical signs, basal metabolic determination is practically impossible in young children. Thus increase in blood cholesterol and decreased creatinuria assume greater clinical importance.

Treated cases may recuperate completely, although many of them require thyroid treatment throughout life. Complete recovery, however, is far from being the rule, as often damage has been done before treatment has been started. At all events, a milder form of the condition is assumed thanks to treatment.

Untreated cases of congenital hypothyroidism never recuperate. These patients die of cachexia or of intercurrent infection. Milder forms are projected into later stages of life, but even in this eventuality death occurs at about the age of thirty, usually from tuberculosis.

Diagnosis. Congenital infantile hypothyroidism presents special problems. The disease must be differentiated from a number of congenital

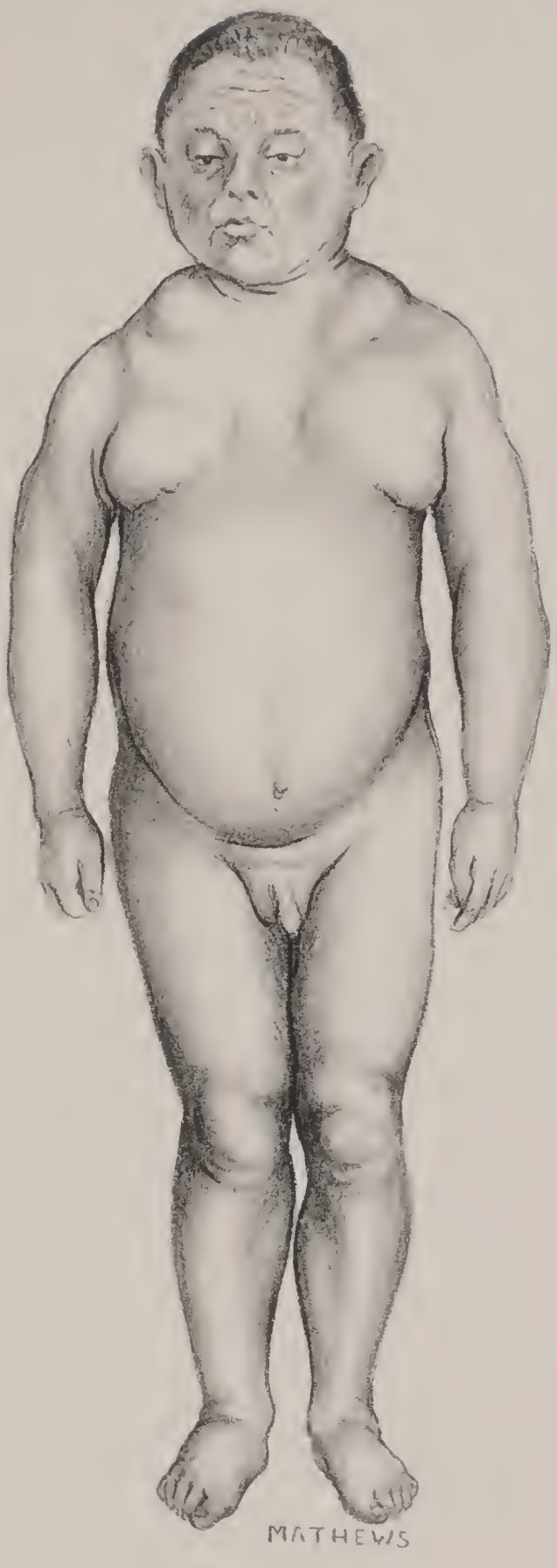


Fig. 3

CONGENITAL HYPOTHYROIDISM (FAGGE'S DISEASE) PROJECTED INTO THE ADULT AGE. NOTE MICROSKELIA WHICH IS NOT NECESSARILY A PITUITARY MANIFESTATION. SUPRACLAVICULAR PADS ACCENTUATED AS IN A CASE OF ZONDEK

deep constitutional disorders, mainly from cretinism, Mongolism, achondroplasia, and primary amentia. Cretinism is distinguished by the endemicity, the intensity of the degenerative process and mental retardation, by various degenerative stigmata, frequent surdomutism, and the inefficacity of thyroid treatment. Primary amentia is distinguished by the absence of symptoms of thyroid involvement (particularly by normal ossification) by the severity of the mental involvement, by degenerative stigmata and the failure of thyroid treatment. In Mongolism the distinctive features are the Mongolian appearance, the narrowness and obliqueness of the palpebral fissures, the happy disposition notwithstanding the mental retardation (in contrast to the apathy of congenital hypothyroidism) and normal ossification. Achondroplasia shows normal mental development and a special morphology marked by a large head, normally developed trunk and abdomen and very short limbs.

Congenital hypothyroidism needs also differentiation from some diseases of infancy which cause deformity and mental retardation. Rickets are distinguished by the special bone lesion, infantile scurvy by the associated hæmorrhages. Congenital syphilis, a rarity nowadays, is characterised by the general dermal and mucous membranous changes such as bullæ on palms and soles, and by snuffles.

Therapeutics. Preventive treatment is of extreme importance, and consists in treating the hypothyroidism and other endocrinopathies of both parents before conception of an offspring, the hypothyroidism and other endocrinopathies of the mother after conception. Many tragedies could be averted by collaboration of the endocrinologist in ante-natal care.

For cure of the disease itself thyroid administration is the basic procedure. Results are often spectacular, but depend on the amount of damage already done by lack of thyroid. Thus the earlier the treatment is begun the greater its chances of success. Technique is similar to that of adult acquired hypothyroidism. The initial dosage is usually 0·01 or 0·02. The full therapeutic dose is usually 0·05 at birth, 0·10 at the end of the first year, about 0·2 up to the fourth year, and not more than 0·3 during the fifth and sixth years. This is of course a rough outline, and cases should be strictly individualised. The maintenance dose varies, and is usually continued throughout life in severe cases, but not continuously.

The diagnostic following up for institution of treatment has certain peculiarities. The assessment of thyroid tolerance is based on the general behaviour, sleep and temperature. Restlessness and insomnia indicate temporary interruption or diminution of dosage. The rectal temperature should be taken twice a day in the course of treatment, and a rise of more than 1° in the absence of another cause such as a digestive upset is also an indication for temporary discontinuation of treatment. Assessment of the efficacity of treatment is made through the clinical picture and through detection of an increase of creatine in the urine and diminution of cholesterol in the blood. Basal metabolism cannot be determined in children.

The only difference between thyroid treatment of this disease and that of

post-natal hypothyroidism is the greater care necessary in the continuous administration of thyroid. The risk of leaving the child without this important hormone during his development cannot be taken. Thus the full therapeutic dose is for a long time the maintenance dose and can be administered either in monthly periods (missing two days each week) separated by one week without thyroid, or on alternate days.

CHAPTER XIV

CRETINISM

(DEEP CONSTITUTIONAL CRETINOIDISM)

Physiopathology and Etiology. Cretinism, one of the most remarkable and best studied diseases, is a deep constitutional disease characterised essentially by occurrence in certain regions of the world. Clinically it is characterised by a syndrome of arrested physical and mental development and goitre, and physiopathologically by an arrest in embryonic development caused by disturbance in the action of genes and organisers. The disturbance of these primary endocrines reacts on the thyroid. Let it be said at once that hypothyroidism is only a part of the general physiopathological and clinical picture of cretinism, and does not by itself constitute cretinism.

Although limited to certain regions of the globe, cretinism should be studied by all. It is a typical deep constitutional disease and to understand it is to possess a basis for understanding the other deep constitutional diseases, particularly as regards the respective role in these diseases of the pre-endocrine regulators of metabolism, the genes and organisers, and of the definite endocrines. Further, the results achieved in this disease show the possibilities offered for many other deep constitutional diseases.

I have had the opportunity of observing cretins in Switzerland with the help of the voluminous but extremely interesting literature on the subject, and although my limited experience of the disease makes a first-hand description impossible, my study of this literature serves to provide a sufficiently complete picture.

There are two major forms of cretinism, the endemic goitre form and the complete cretinic form.

In the endemic goitre form the outstanding and even sole manifestation is the goitre. That endemic goitre is a form of cretinism is shown by its existence in cretinic regions—even although the endemic goitre zone often seems more extended than that of complete cretinism—and by the occurrence of simple endemic goitre and complete cretinism within the same family.

The complete form of cretinism shows the whole picture of deficient physical and mental development. Goitre exists in some cases but is absent in others. For this reason many authors have sub-divided complete cretinism into a goitrous and non-goitrous form, a sub-division which complicates description and is unnecessary, especially as numerous intermediates occur between the cretin without goitre and even without thyroid, the cretin with some goitre

nodules and the cretin with distinct goitre. It has been remarked, however, that in full cretinism with goitre the systemic manifestations are milder.

The clinical syndrome of cretinism was first described in the sixteenth century by Paracelsus, who pointed out the association of goitre and mental deficiency in this disease. Subsequent studies of the same subject by Felix Platter and Wolfgang Hoefer developed this description. In the eighteenth century great progress was made by Vicenze Malacarne and principally by Foderé, whose descriptions are so accurate that they can be read with profit even to-day. In the first half of the nineteenth century clinical study advanced greatly, mainly through the work of Guggenbuhl and Maffei.

Cretinism has been regarded as a hypothyroidean condition by many authors after discovery of the role of the thyroid in congenital myxœdema (sporadic cretinism) by Fagge, in adult myxœdema (" cretinoid condition of middle-aged women ") by Gull and the excellent work on thyreoprivic cachexia by Kocher and the Reverdins. By analogy the thyroid conception was extended to cretinism by Sir Felix Semon and others. But reasoning by analogy is a dangerous process. This thyroid conception was justified at that time, that is in the 'eighties, because the only alternatives were vague notions of degeneration and atavism derived from the theory of evolution. Nowadays, however, knowledge of genes and organisers and a better study of the deep constitutional diseases allows of another conception leading to a better understanding of the " sui generis " clinical history of cretinism.

The purely hypothyroidean view elaborated by the unicists of the 'eighties has never satisfied the clinicians. Between cretinism and the hypothyroidism most nearly approaching it, the congenital myxœdema, there are differences pointing to a special physiopathology. The striking endemicity of cretinism gives it distinct independence. The clinical picture shows great differences, although it is true that in cretinism many hypothyroidean manifestations are seen and the thyroid is involved. The low stature, the slow physical development, the many degenerative stigmata, the slow chronicity and permanence of the condition differ from the deformities, obesity and generally repulsive appearance of the rare cases of congenital hypothyroidism, such as I saw in my young days in Bourneville's clinic at the Paris hospital of Bicetre. The mental picture also differs in the two diseases, as will be shown later. Iodine is beneficient in cretinism, particularly from the preventive aspect. In myxœdema it has no action. Thyroid medication works miracles in myxœdema, but is useless and even noxious in cretinism.

To explain these differences many authors have abandoned the purely hypothyroidean conception for a wider polyglandular view holding the pituitary and parathyroids as well as the thyroid responsible for cretinism. Even this conception, however, although it confers nosographical independence on cretinism, is insufficient and theoretical.

On the basis of recent developments in genetics and embryology cretinism can be accepted as a deep constitutional disease, *i.e.*, a disease of embryonic development in which noxious factors have acted on the first regulators of

body chemistry and thus of embryonic development, on the genes and organisers. The genes or organisers for the brain and thyroid are particularly and concomitantly involved, but also the genes and organisers for other parts of the body, which explains the existence in cretinism of disturbances in the development of other organs and parts of the body, disturbances known even to-day as " stigmata of degeneration " although the atavistic theory embodied in this term has long since been exploded.

This disturbance does not seem hereditary. In other words, a gene abnormal for the thyroid, nervous system or other parts of the organism and thus making for their cretinoid development is not transmitted through heredity. The problem is not solved, but for the endemic goitre form of cretinism at all events it has been shown that healthy women settling in villages in which cretinism prevails give birth to cretin children (endemic goitre form), and that conversely women with cretinic endemic goitre settling in places free from cretinism give birth to normal children (Engsten).

The disturbance is thus due to factors of environment which set up metabolic disturbances in the mother. In their turn the metabolic disturbances cause the possible mutation of genes and the disturbance of the organisers which result in the developmental disease, cretinism.

What are the factors that, acting upon the mother, set up these metabolic disturbances? Little is yet known about them. The only definite finding is that they exist in certain regions, often in very limited regions. There are particular villages and even particular houses in which cretin children are born, whereas in neighbouring villages or houses the children are born normal.

The nature of these etiological factors is known principally for the endemic goitre form of cretinism. Here the outstanding factor is iodine deficiency, arising either from deficient iodine intake (the only demonstrated fact) or from deficient iodine utilisation, principally absorption. Iodine deficiency in drinking water is a well demonstrated fact and an essential characteristic in regions of cretinism. Excessive calcium intake and thus excess of calcium in water also has been incriminated for the endemic goitre form of cretinism, but the fact has not been well established nor is the possible mechanism clearly understood.

Cretinism is restricted to certain districts. It is encountered in the central Alps, the hilly parts of Germany, the Carpathian mountains, the Pyrenees and the Himalayan regions. It is not confined to mountainous and hilly parts, however, but is met in such valleys as the Valley of Aosta and those of the Sudan, Persia and Russia. In the United States the endemic goitre form of cretinism occurs in the region of the St. Lawrence, the Great Lakes Basin extending through Minnesota and the adjacent parts of Canada, and the Pacific North West. In South America it is encountered in the Andean Mountains. According to Marine and Carlson in districts of endemic goitre comparable changes are found in animals.

In many of these regions the disease is a social scourge. In Styria there are 1,000 cretins per 100,000 inhabitants. In certain school statistics in Tyrol and Southern Bavaria the proportion is 40–50%, in some Swiss districts 90%.

Clinic of Endemic Goitre Cretinism.

The leading manifestation in endemic goitre is the goitre. The cretinoid nature of the goitre is amply demonstrated by its occurrence in endemic cretinism regions and in families whose other members show other forms of cretinism.

The goitre is apparent in some cases at birth. Usually, however, it is detected later. It increases progressively and at a certain stage, generally after puberty, is arrested in its development and remains the same thereafter throughout life. It often shows as a very large deforming thyroid tumour, much larger than in sporadic goitre. Like the simple sporadic goitre previously described, it may cause pressure symptoms, and degenerate into cancer. Whether, like sporadic simple goitre, particularly of nodular form, it gives rise to a toxic adenoma syndrome is very doubtful.

Anatomically endemic goitre may be of parenchymatous diffuse form and even show the histological picture associated with thyroid hyperfunction (as in Graves' disease) but without clinical manifestations of hyperthyroidism, recalling thus the thiocyanate goitres. Such a goitre is found at puberty. Usually, however, it is of colloid type with production of cysts through coalescence of many distended acini. The pressure of the cysts increases the atrophy of the adjacent parenchyma, which is often replaced by hyaline scar tissue, but a more or less normal thyroid can be found between the normal cystic or fibrotic areas.

In pure cases of this incomplete form of cretinism, the endemic goitre form, there are no symptoms other than those due to the thyroid tumour. In certain cases intermediate between the two main forms of cretinism, however, symptoms indicating thyroid insufficiency occur. Hyperthyroidism, as already stated, is not found clinically in endemic goitre.

The course of endemic goitre is chronic. It lasts throughout life, and apart from cases of pressure symptoms or malignant degeneration it does not shorten the life of the patient. In some cases it retrocedes with iodine treatment.

Clinic of Complete Cretinism.

Complete cretinism is constituted essentially by a general syndrome of morphological under-development, mental deficiency and certain other nervous and organic disturbances. Goitre may or may not exist. A sub-division has been attempted on the basis of the presence or absence of goitre, but this is an unnecessary complication of the description. There are various degrees of cretinism, goitre usually existing in milder forms but not in the more severe forms. With these reserves the complete description is given.

Although complete cretinism (which for the sake of brevity shall be termed cretinism, as it is the real form of the disease) has been shown to be congenital in the delineation of the physiopathology of the condition, it is not recognised early except in the rare congenital goitrous forms. In the first year of life the only sign is lack of interest in the surroundings and laziness of movements. In the second year the teeth fail to develop, and

the child cannot walk. After that, disturbances of development are more distinct. Growth does not proceed normally. The mental development lags. Puberty does not occur at the usual time. The sexual characters develop slowly.

After the puberal age all development stops, and cretinism is established. The individual will remain in the same condition for the whole of his life. There occurs no aggravation but no retrogression of the morbid manifestations.

The General Syndromes. *Morphological syndrome.* Height is much under normal, showing dwarf proportions. The cretin has an abnormally large head, an abnormally long trunk and abnormally short legs.

The head is characteristic, but only in severe cases. In mild cases it shows the features of the race to which the cretin belongs (the Alpine race, in the case of European cretins). The true cretinic head is very large. The cheek bones protrude, the nasal root is depressed, the frontal and occipital protuberances are very thick, and the jaw is under-developed. The skin is not alabaster-like as in hypothyroidism, but grey-yellow with tendency to browning (it should be remembered, however, that most cretins live in the open air). The facial expression is that of a monkey or pig. Mental deficiency, idiocy and imbecility are written over all traits. There is often an expression of placidity, interrupted by an idiotic grin. The skin is intensely wrinkled and dry.

The teeth do not show the frequent caries found in hypothyroidism. According to de Quervain, Mayrhofer even mentions a degree of immunity to caries in such individuals. There are positional defects due to maldevelopment of the jaws. The teeth erupt slowly, a hypothyroidean stigma.

Hair is coarse and hard but does not fall as in some cases of hypothyroidism.

In goitrous forms the goitre gives a peculiar stamp to the habitus.

This morphological syndrome differs from that seen in congenital hypothyroidism.

Mental syndrome. Mental deficiency is the great essential characteristic. It varies in intensity, and three types can be distinguished, the completely helpless cretin, the half-cretin, and the semi-adapted cretin. The completely helpless cretin is a human vegetable. His intellectual level is zero. He may have a certain memory of persons and of material comforts such as eating sweets, but on the whole he lies helpless throughout life. The half-cretin is sufficiently developed to do outdoor and house work under supervision, but he cannot work independently. He can make himself understood in a primitive way. The semi-adapted cretin can learn to read and write and to do simple manual work. He has sufficient memory to go through life. Such cretins marry, with individuals of similar level or with healthy persons, and have descendants.

Certain peculiarities distinguish the mental deficiency of the cretin from that of other diseases, including hypothyroidism. First of all, despite the severe mental defects, memory of places and persons is conserved. Both semi-adapted and half-cretins can find their way about. They remember persons, particularly those who have been good to them. Next, although cretins react

very slowly to all stimuli they may make remarks which could be taken as village humour or even commonsense.

The second outstanding mental feature of the cretin is a characteristic torpor in action and reaction. Although the cretin in some cases flies into a temper without comprehensible reason, screams and commits violent acts, he is usually calm, apathetic and unmovable. He seems not to have eaten of the fruit of the tree of knowledge, and can neither invent nor do any harm to his fellow-creatures. He is extremely happy, optimistic in spite of his sombre facial expression. Time does not count for him. He lives for the moment, and for the moment alone. Thus the terms " Christian " from which " cretin " is derived, and " innocent " have been conferred on cretins throughout the ages, and indeed the cretin is the most likeable of all mental defectives. I have seen semi-adapted cretins in Swiss villages watching the work, play and drinking of their healthy compatriots. The apathetic aspect of these cretins and the remarks they occasionally made gave the impression of sense and a certain rural philosophy. The cretin is very conservative. Having a peculiar need of security he is a good subject and never revolutionary.

When to these outstanding psychological characteristics are added certain mannerisms, such as the mania for collecting various objects with which he fills his cupboards and a tendency to imitation, a great difference is apparent between the mental make-up of the cretin and that of the congenital hypothyroidean. It is true that this psychological study of the cretin is incomplete. It is based on the Alpine cretins, and probably the social environment of the cretin plays an important role in the fashioning of his psychology, but even with these reserves the clinician accustomed to judging nuances gets the impression that he is dealing with a disease sui generis.

Sexual syndrome. In male complete cretins the genital organs are not generally undeveloped. Even in cases where the sexual functions are in abeyance this is not indicated by the morphology of the sexual characters. Sexual deficiency is very marked, but cretins of mild degree can have intercourse and procreate. Even in such cases, however, potency and libido are low.

The same sexual deficiency occurs in cretin women. Amenorrhœa and sterility are noted in severe cases, hypomenorrhœa in mild cases. Mild cretins, however, can bear children to cretins or healthy individuals. Female cretins are more provocative than their male counterparts, and therefore give more trouble from this point of view in institutions. On account of the narrow pelvis, delivery is often difficult.

The Organ Syndromes. *Nervous syndrome.* This is a major syndrome in complete cretinism. It is due to the primary developmental disturbance of the central nervous system, and constitutes the essential difference from the clinical picture of hypothyroidism. Morbid anatomists whose work has been summarised and completed by Wegelin have described intense lesions of the central nervous system. The details of these lesions show but little agreement, particularly as regards the frequency of hydrocephalus. This was considered a major anatomical feature by Wallmann, Rösel, Virchow, Schulz and

Zingerle. Wegelin attributes less importance to this feature, although he has found it in 14 out of his 29 cases, mostly, however, in mild forms.

Motor functions are disturbed, indicating maldevelopment of the pyramidal system. In severe cases motility is nearly completely impaired. These individuals lie like so many inert masses, " rubis indigestaque moles." When they are pulled up they fall like logs. It is as if the whole motor apparatus from the cortex downwards is destroyed. In the usual more moderate cases walking is disturbed. It is a tottering waddling gait. Such disturbances can be caused by the hip lesions so frequent in cretinism, but they exist also independently of these lesions. In some cases (de Quervain) Little's syndrome has been described.

Reflexes are abnormal. The patellar reflex, according to de Quervain, is exaggerated in 47 per cent. of cases, the ankle reflex in 17 per cent. A positive Babinski sign is found in 17 per cent. of cases. The skin reflexes, abdominal and cremasteric, which are in fact cortical reflexes, are diminished.

Speech is greatly disturbed. It is thick, monotonous, unintelligible, often perceived as a muttering, and understood only by those accustomed to dealing with cretins. The vocabulary is very limited. Such speech defects are not parallel with defects in hearing, when these exist, and point to a central origin.

Deafness is very frequent, and many authors even regard it as an oligosymptomatic cretinism, *i.e.,* the sole manifestation of the disease. Laufner's statistics have shown the frequency of deaf-mutes in the endemic region of Bern. According to the statistics of Wydler, among distinct cretins there is complete deaf-mutism in 42 per cent., deafness with incomprehensible speech in 32 per cent., incomprehensible speech with normal hearing in 25 per cent. The deafness is due mainly to disturbances of the cortical auditory centres and to the general cortical defect. In very rare cases it is explained by a middle otitis.

McCarrison has described as " nervous cretinism " cases in which tetanic attacks and other convulsive manifestations occur. He attributes such cases to parathyroid insufficiency. His work has not been confirmed in the more extensive observations of de Quervain.

Strabismus also is encountered but not frequently. It may be a hypothyroidean manifestation.

Other syndromes. Retardation in the appearance of the nuclei of ossification is very frequent. Coxarthritic lesions exist, often in intense form. They show the picture of Perthes' osteochondritis deformans juvenilis. The pelvis is narrow.

The muscular system is badly developed in severe cretinism but may be normal in most others, particularly in those who work in the fields and develop their muscles by exercise. There is a distinct tendency to hernia.

The heart is usually enlarged, but less than in myxœdema. The capillaries, as demonstrated by capillaroscopic studies, are distended, and although this symptom is not pathognomonic it is constant. No cretin and no case of distinct myxœdema shows a normal capillary picture, whereas Mongolism,

achondroplasia and pituitary adiposogenitalism show pictures normal from this point of view.

Digestive disturbances are not very marked.

Course of the Disease. Full cretinism develops progressively as regards its clinical manifestations until shortly after puberty and is then arrested. From that time onwards there is neither amelioration nor aggravation. With care, cretins can live a normal span and die of old age. In severe cases, however, death occurs earlier through intercurrent infections.

Much can be achieved therapeutically in helping cretins to happiness, comfort and adaptation to their limited horizon of life. In 1855 Blacker referred to a Dr. Odet who was a cretin " in the first stage " but as the result of most careful attention recovered so much as to be able to write an essay on cretinism published at Montpellier in 1805.

Therapeutics. Prophylactic treatment is based on iodine administration and general hygienic measures. It cannot be given in detail here, although constituting one of the most interesting chapters in social medicine.

The basic procedure is group treatment, with re-education in special colonies or institutions. Next come general constitutional medicines bearing particularly on hygiene and diet, which have proved very effective. Iodine preparations are administered, but without notable result. Thyroid is badly tolerated.

Corvisart said that medicine is not the art of curing patients but the art of treating them with the object of curing, relieving or satisfying them. In this sense much has been done for cretins, and these results sound an optimistic note for all patients with deep constitutional diseases, to whom medicine has hitherto adopted the attitude of the ancient Spartans less the courage of throwing them over the precipice of the Taygetos. Preventive as well as general constitutional measures have given much help, and physicians in regions of cretinism who have tackled the problem can be inspired with courage from these results.

CHAPTER XV

HYPERPARATHYROIDISM

Hyperparathyroidism is a disease characterised predominantly by hypersthenic reaction of the parathyroid system.

In describing hyperthyroidism two separate diseases based on thyroid hyperfunction were delineated, thyroid toxic adenoma in which hyperthyroidism originates in the local thyroid tumour, and Graves disease or cerebro-pituitary hyperthyroidism in which the hyperthyroidism originates in an excessive impulse from the cerebro-hypothalamic centres.

The same pattern exists for hyperparathyroidism. Here also there are two diseases, toxic hyperparathyroid adenoma in which the hyperparathyroidism originates in the local parathyroid tumour, and cerebro-pituitary hyper-

parathyroidism in which the hyperparathyroidism originates in an abnormal impulse of the cortico-hypothalamic centre of the parathyroid system. In order, however, to simplify description, the term hyperparathyroidism here includes both parathyroid toxic adenoma and cerebro-pituitary hyperparathyroidism in the same chapter, although the description bears principally on parathyroid toxic adenoma which, in contrast to thyroid toxic adenoma, is the most distinct and best studied of diseases based on parathyroid hyperfunction.

The most prominent manifestation of hyperparathyroidism, the osteopathy, was first described by J. J. Courtial in 1700 (according to Professor J. Beatie) and after him by many, including Engel (1864), Davies Colley in 1884, and ultimately by von Recklinghausen in 1891. This brief historical note indicates that the term Recklinghausen's disease is not justified. The connection of this osteopathy with the parathyroids was first considered in 1907 by Erdheim, who regarded the parathyroid tumour as secondary. In 1925 Mandl demonstrated the hyperparathyroid mechanism of the osteopathy, and thereby introduced the disease hyperparathyroidism into nosography. In this country it has been studied by Donald Hunter.

Physiopathology and Etiology.

The hypersthenic reaction of the parathormone system is the basic disturbance of the constitutional regulatory system resulting in the disease hyperparathyroidism. The hypersthenic reaction may originate in the glandular centre of this system from the presence of a hypersecreting parathyroid adenoma and give rise to a primary glandular hyperparathyroidism, or it may originate in the diencephalic centre of the parathyroid system and give rise to a cerebro-pituitary hyperparathormonism.

Glandular Hyperparathyroidism (Toxic Parathyroid Adenoma). This results from a hypersecreting parathyroid tumour, mainly an adenoma. The primary cause of production of such adenomas is not known, but judging by thyroid adenomas they may be regarded as a terminal reaction of the whole parathyroid system beginning at the diencephalon. The only fact in favour of this conception is the coincidence of pituitary basophile adenoma and parathyroid adenomas, sometimes observed. Whatever the original impulse towards adenoma formation, however, parathyroid adenoma once constituted develops by itself.

All parathyroid adenomas are not endocrinic, *i.e.*, not toxic. Non-toxic parathyroid adenomas, which number 50 per cent., show no histological differences (at all events with present technique) but differ in their dimensions. In Benjamin's case the tumour reached the volume of a child's head, and Bland Sutton described a fatal case of compression of the trachea from a voluminous parathyroid non-toxic adenoma. Here also analogies with goitre are evident. There are thus simple parathyroid "goitres," pressure parathyroid "goitres," and toxic parathyroid "goitres."

Endocrinic or toxic parathyroid adenomas are smaller, scarcely larger than a walnut. The adenoma is usually solitary in endocrinic cases but two or more

at the same time have been encountered. They originate in any of the normal four parathyroids but also in ectopic parathyroids, a fact that raises clinical and operative difficulties. Ectopic adenomas have been found between the œsophagus and the thyroid, under the left clavicle, in the anterior and posterior mediastinum.

Their histology contains many discrepancies, because it is usually difficult to distinguish anatomically between adenoma and parathyroid hyperplasia, which is a manifestation of cerebro-pituitary hyperparathyroidism. Certain authors hold that parathyroid adenomas are composed of only one kind of parathyroid cell, the water clear cell. According to others both water clear and oxyphile cells are found. At all events, the parathyroid cells in these adenomas are increased in volume as well as in number.

In exceptional cases a parathyroid carcinoma has been found at the origin of parathyroid hyperparathormonism Cases have been described by Wilder (with anatomical study by Wellbrook) and by Meyer and Ragins.

Cerebro-pituitary Hyperparathyroidism. This form is less well known and its conception is more of a working hypothesis, particularly for understanding of hyperparathyroidism with hyperplasia. The accepted etiology is an interplay of a genogenic factor of parathormone system inferiority (abnormal lability) with various environmental conditions. Among the latter calcium deficiency is the best demonstrated, and in fact in diseases with calcium deficiency such as rickets and osteomalacia, and in pregnancy (when the body is depleted of calcium by the fœtus) parathyroid hyperfunction occurs. This probably originates in an abnormal compensatory reaction of the whole parathyroid system beginning at the diencephalon with the object of re-establishing normal calcium balance in the blood. Similarly, in certain nephritic conditions when hyperphosphatæmia occurs through deficient excretion of phosphorus, the whole parathyroid system beginning at the diencephalon reacts so as to drain more calcium from the bones and re-establish ionic balance in the blood. In such cases also parathyroid hyperfunction occurs, and this hyperparathyroidism secondary to chronic nephritis has to be distinguished from nephritis secondary to hyperparathyroidism due to other causes. Other factors acting on the diencephalic centre of the parathormone system and causing a cerebro-pituitary hyperparathormonism—factors such as diencephalitis or psychogenic conditions—are more doubtful.

In cerebro-pituitary hyperparathormonism the intense diencephalic drive on the parathyrotropin-secreting antepituitary cells is manifested morphologically by the hyperplasia of these cells. This hyperplasia usually involves all the parathyroids, whereas adenoma is localised as a rule in one gland only. It is characterised by multiplication of the parathyroid cells, both water clear and oxyphiles, but without augmentation of the volume of these cells. It is often difficult to differentiate it from an adenoma but according to some histologists adenoma involves only the water clear cells and these are not only multiplied in number but also augmented in volume.

Metabolic Disturbances in Hyperparathyroidism. The disturbances of body chemistry following parathyroid hyperfunction bear on calcium and phosphorus metabolism.

Excretion of phosphorus is first intensified and much phosphorus then appears in the urine, whereas the blood and the body in general are poor in this element. Hence hypophosphatæmia.

Calcilysis, the yielding of calcium from its depots, the bones, is intensified next. This calcium passes into the blood with the object of re-establishing the osmotic equilibrium disrupted by the loss of phosphorus. Hence hypercalcæmia, and when too much calcium accumulates in the blood it is excreted in the urine. Hence hypercalciuria.

These disturbances of body chemistry react mainly on the bones and kidneys, and on other systems. The bones are the first to suffer because they are depleted of their calcium. As experimental work has demonstrated (Jaffe, Bodansky and Blair) there occurs first multiplication of osteoclasts, which cause absorption of bone and the picture of generalised osteitis fibrosa. Later, as in Selye's experiments of parathormone intoxication, when tolerance has developed the osteoblasts multiply and increase the solidity of the bones, which resemble marble. In man the decalcification of bones makes them porous, full of osteoclasts, and a rarefying osteopathy with cysts and clefts appears. As a defensive process osteoblasts develop and lay new bone here and there, thus adding a process of condensing osteopathy. In some cases this secondary osteoblastic proliferation reaches such a degree that benign tumours of the bone tissue develop osteoblastoma with giant cells. Osteoporosis and cysts render the bones very fragile, and fractures occur more or less spontaneously. The bone lesions, including the fractures, result in definite deformities.

The kidneys also are frequently disturbed, primarily because the metabolism of the renal cells is disturbed by the altered calcium and the phosphorus content of the pericellular fluids, and secondarily from precipitation of calcium, which is excreted in excess.

The primary event seems to be a necrotic disturbance of the interstitial tissue of the kidneys, due to the alteration of the pericellular ionic equilibrium. This necrosis constitutes a locus minoris resistentiæ, and calcium abundantly carried by the blood is deposited. Thus interstitial fibrosis, calcification, infiltration by lymphocytes and plasma cells result. In some cases the glomerules also are involved by this primary metabolic " degenerative " process, although this seems rare. The vessels of the kidneys show calcification of their walls and hyaline degeneration, but this also seems an unimportant process.

As a result of the interstitial lesions of the kidneys the tubules are narrowed in some places, and thus cystic dilatation may occur. The cells of the tubules also are altered. Calcium is deposited in the lumen of the tubules and forms cysts. This whole process of hyperparathyroid nephritis, a typical metabolic nephritis, has been described by B. Chown and his collaborators, W. A. D. Anderson and W. A. Oliver.

Besides the interstitial nephritic process a lithiasic process occurs and often

dominates. It consists in the production of stones of the kidneys due to precipitation of calcium in the chalices or pelvis of the kidney. Stasis due to fibrotic lesions favours calcium formation.

The circulatory system is involved also through the same twofold mechanism of primary cellular disturbances due to change in the pericellular fluids and calcium precipitation. Hyaline degeneration, calcification and narrowing of the arteries occur. In acute hyperparathyroidism the heart has been found to show foci of necrosis and of calcium salt infiltration. The digestive system shows disturbances due to the general metabolic derangement engendered by hyperparathormonism.

Symptomatology—The Complete Form.

Mode of onset. In certain rare cases the disease may develop relatively rapidly, as in Lander's case, in which cysts of the calvarium and jaw were already present in six months. In general, however, the disease is insidious in its development, and onset is slow. The condition smoulders for many years before the patient seeks medical aid. In one of Albright's patients there was reason to believe that the disease had existed for 36 years before its recognition.

In 72 per cent. of cases the initial symptom complex for which the patient seeks advice consists of pseudo-rheumatic pains of back and limbs, particularly severe lumbago. It is important to remember this mode of onset of hyperparathyroidism in differential diagnosis of backache. In other cases the first presenting symptoms are pathological fractures, tumours of the maxilla, bone swellings, disturbances of gait, muscular weakness. Less frequently the initial symptoms are urinary, consisting in polyuria with polydipsia and renal colic, or digestive such as nausea, vomiting, epigastric pain. Loss of weight accompanies any of these symptom complexes in 10 per cent. of cases and may even be the dominant feature.

The disease is constituted of the following syndromes:

Locomotor Syndrome of Osteopathy Fibrosa Cystica. Principal symptoms are pain, peculiar deformities and functional incapacity. The pains are those usually described as rheumatoid. They are felt in back, legs and hands and are frequently associated with stiffness of the joints. They are localised distinctly in the bones and are aggravated by movement. The tenderness of the bones of the hands makes handshakes painful.

The bone deformities correspond to the cysts and to the fractures. Cysts are detected as bone swellings occurring mainly on jaws and tibia. At onset they may be solitary and painless but later become multiple and tender. The results of fractures are manifested by anterior bowing of the legs, spinal curvature, collapse of the cage of the pelvis, flaring of the costal margins, genu valgum. The progress of decalcification is such that even unimportant movements such as turning in bed or a violent cough may result in bone fracture.

Functional incapacity at onset is due to pain, later to bone deformities. Even at onset the pain in the back by its intensity keeps the patient in bed. Later, when fractures and deformities occur, incapacity may be almost com-

plete. In the last phase of the disease the patient is totally bedridden, incapable of doing any movement even in bed, prone to multiple fractures, deformed. It is one of the most terrible sights.

Röntgenological investigation reveals as general manifestations decalcification and cysts, sometimes with a reactive new bone formation. The calvarium shows osteoporosis and appears to be thinned but in some cases the new bone appears on the skull, thickening it and giving the appearance of Paget's disease. Cystlike areas are found in the skull bones. The teeth show no abnormality because they are essentially resistant to decalcification but the roots may be absorbed. The long bones of the limbs show the most characteristic lesions. Cysts are seen, as well as osteoporosis manifested by progressive cortical thinning. Fractures also may be evident in association with excess of callous formation. The vertebræ, when involved, are osteoporotic and granular. They may be softened and collapse, leading to scoliosis and kyphosis.

Besides the bones other parts of the locomotor system are involved. Arthritis with ankylosing lesions has been described by Leriche as an oligosymptomatic form of hyperparathyroidism, a conception not usually accepted. Muscular involvement is more distinct, and hypotonus of muscles and ligaments has been observed. A patient of David P. Barr was able to sleep with her head on her ankles or with both ankles thrust under her head. Muscular weakness exists in about one-half of cases and adds to the difficulty of walking.

Urinary Syndrome of Nephropathy and Renal Lithiasis. The nephritic syndrome may coincide with osteopathic manifestations or occur independently. In its mild form it is characterised by polyuria, pollakiuria and a slight albuminuria, a symptom which may precede osteopathic manifestations. Pollakiuria was so pronounced in a case of David P. Barr that it led the physician to diagnose inflammatory cystitis. In more severe cases the complete symptomatology of Bright's disease exists with retinal exudates and hæmorrhage, cardiac enlargement, peripheral œdema, but without marked hyperpiesia. Such cases terminate with the complete uræmic syndrome. A patient of Benjamin M. Baker and John E. Howard with uræmia and general symptoms of hyperparathyroidism experienced great relief after partial parathyroidectomy. As in hyperparathyroid nephritis calcification is marked this condition gives a characteristic röntgenological picture of nephro-calcinosis.

The renal lithiasic syndrome, which has been encountered in 70 per cent. of cases of confirmed hyperparathyroidism, shows the usual picture of renal lithiasis. It may coincide with interstitial nephritis or occur independently.

Digestive syndrome. Outstanding symptoms are anorexia but principally vomiting. Anorexia is noted in 12 per cent. of cases. Vomiting occurs in spells and may dominate the picture. Morelle reported the case of a woman hospitalised for intractable vomiting taken for intestinal obstruction. Calcæmia of 19·7 mms. per cent. was detected, hyperparathyroidism suspected, and on operation a parathyroid adenoma was found and extirpated.

The vomiting is under the direct influence of the endocrine disturbance. Patients with parathyroid adenomas who may have experienced nausea and vomiting for months are rid of their symptoms abruptly after parathyroidectomy. An accidental over-dosage of parathormone, as in the case of Lowenburg, Harris and Ginsberg, has provoked nausea and vomiting.

Biochemical Symptoms. Hypercalcæmia and hypercalciuria, hypophosphatæmia and increase in phosphatase are outstanding.

Hypercalcæmia is constant. Instead of the normal 10 milligrams of calcium per 100 cc. figures ranging from 12·5 to 30 are found. Even when the figure is normal, as often happens, ionised calcium is raised (and, it must be repeated, this is the only calcium of import biologically). The degree of hypercalcæmia depends greatly on renal permeability, and may be low in severe cases if elimination is rapid and relatively high in mild cases if the kidneys are involved. Hypercalciuria is the result of hypercalcæmia but of course depends also on renal permeability. It is to be noted that in hyperparathyroidism urinary calcium is not only high but is relatively higher than fæcal calcium. Normally 10 to 30 per cent. of calcium is excreted in the urine and 70 to 90 per cent. through the fæces, but in hyperparathyroidism the proportion is reversed.

Hypophosphatæmia and hyperphosphaturia indicate disturbance of phosphorus metabolism initiated by the parathormone drive which increases phosphorus excretion.

The increase of blood phosphatase is important. This is an enzyme capable of splitting phosphorus compounds and liberating organic phosphorus. Normally, according to Bodansky, 1·5 to 4 units are found in adults and 5 to 12 units in children. In hyperparathyroidism higher figures occur.

The metabolic syndrome of hyperparathyroidism must be evaluated in its totality and in the light of the totality of symptoms. Hypercalcæmia, hypercalciuria, hypophosphatæmia, hyperphosphaturia and increased phosphatase are found in many conditions. It is their combination and the coincidence of other symptoms of hyperparathyroidism that are specific. Many mistakes arise from consideration solely of hypercalcæmia, for instance.

Course of the Disease. Local or neoplastic hyperparathyroidism is an insidious and protracted disease. It cripples but does not kill. As the crippled hyperparathyroidean is a fragile vessel, however, it is unusual for him to live, if not operated, for more than twelve years. Operation improves these patients and gives them a longer life.

Special Forms.

The *acute forms* are rare. A case has been described by Lowenburg, Harris and Ginsberg from overdosage of parathormone. It was characterised by vomiting, listlessness, extreme mental depression, high irregular fever and tachycardia. Acute hyperparathyroidism has been well studied experimentally, and should not be confused with an acute exacerbation of the common form.

Formes frustes also have been described. They consist in osteoporosis and renal disturbances, but their hyperparathyroidean nature is demonstrated by the biochemical findings.

Oligosymptomatic forms are the most interesting. Hyperparathormonal nephritis, hyperparathormonal renal lithiasis and hyperparathormonal osteoporosis (Albright) have been well demonstrated. In these conditions the nephritis, the renal lithiasis and the osteoporosis are characteristic clinical syndromes of hyperparathyroidism. The biochemical syndrome of hyperparathyroidism is seen, or a parathyroid adenoma or parathyroid hyperplasia, and parathyroidectomy has given good results. Hyperparathyroidism should be remembered in the differential diagnosis of chronic nephritis, renal lithiasis, osteoporosis. According to Burney and Minz, 5 per cent. of renal lithiasis are of hypoparathyroidean origin.

Many other oligosymptomatic forms have been described but on more speculative grounds. They comprise not the syndrome usually encountered in hyperparathyroidism but one foreign to the general symptomatology of the disease here described. Their hyperparathyroidean nature is accepted on the basis of hypercalcæmia and the good effects of parathyroidectomy. On this basis a hyperparathormonal chronic rheumatism of ankylosing type (Leriche), a hyperparathormonal endarteritis obliterans (Bastai and Doglioti) and a hyperparathormonal scleroderma (Leriche) have been described. The hyperparathormonal nature of these conditions, however, has not been sufficiently proved. Hypercalcæmia is not sufficient to characterise parathyroid hyperfunction. Parathyroidectomy may act through a mechanism of vegetative shock (the Umstimmung of the Germans), not through that of diminishing parathormone secretion. In fact, certain hyperparathormonal rheumatisms have improved when, by mistake, thyroid tissue or fat, not the parathyroids, has been removed by operation.

Marble bone (Albert Schönberg disease) also has been regarded as a form of hyperparathormonism on the basis of Selye's experiments, and Petin, Policard and Dufourt's finding of parathyroid hyperplasia in one case. However, in this disease characterised by increased density of the bone, calcæmia is normal (H. Bernhard, McCune and Bradley), and it is probably a genetic disease.

Diagnosis.

Hyperparathyroidism is often misdiagnosed because there is no wide knowledge of this disease and many other morbid conditions may simulate it. The characteristics which serve as leaders in differentiation are the totality of symptoms of the disease and particularly radiological signs and biochemical findings.

Differentiation from lumbarthritis often enters into consideration at the onset, which is marked by intense lumbar pain. Diagnosis is based on the detection of the generals and biochemicals of hyperparathyroidism.

Paget's disease is another difficult problem of differential diagnosis. In

this disease there are neither cysts nor giant cell tumours. Radiologically the cortex of the long bones is thickened and laminated, with a special cottonwool appearance. However, radiological differentiation is often difficult. It should be remembered that in Paget's disease, contrary to the findings in hyperparathyroidism, bone deposition dominates over bone resorption. Calcæmia is normal, and blood phosphatase shows much higher figures than hyperparathyroidism.

Multiple myeloma is very hard to differentiate, for clinical, radiological and even biochemical manifestations are similar to those of hyperparathyroidism. The findings of Bence Jones' protein, however, tilts the balance in favour of multiple myeloma, and biopsy makes definite diagnosis possible.

The so-called renal dwarfism with rickets is even more difficult to differentiate. The only leader is the time of appearance of the nephritic manifestations, which in renal rickets precede osteitic lesions and in hyperparathyroidism follow them. Many cases believed to be renal rickets are really cases of hyperparathyroidism.

Other diseases with bone deformities are easier to differentiate. In osteomalacia there are neither cysts nor hypocalcæmia. In common rickets the bone deformities are quite different (hyperplasia of the parathyroids without hyperfunction has been found in this condition as a reaction to exogenous calcium deficiency). Osteopsathyrosis is distinguished through its hereditary nature, the existence of blue sclera and of deafness. Solitary cysts of the bones are distinguished by their solitary character and the absence of hypocalcæmia.

The existence and frequent predominance of nephritic and renal lithiasic symptoms necessitate differentiation from other nephritic and nephrolithiasic conditions.

Albright's Syndrome of Osteitis Fibrosa Disseminata with Precocious Puberty and Pigmentation. This syndrome, of which the clinical picture is indicated in the definition, is differentiated by the presence of female precocious puberty and pigmentation. In my opinion it can be considered as a bi-hormonal syndrome of hypothalamic origin (Albright has found is one of his cases lesions of the corpus mammillare). A cerebro-pituitary hyperparathyroidism is responsible for the bone lesions and a coincident cerebro-pituitary hyperœstrinism for the female precocious puberty and the pigmentation.

Simple Parathyroid Hyperplasia. The metabolic disturbances due to rickets, pregnancy and nephritis already described may determine a simple parathyroid hyperplasia without hypersecretion, instead of generating a total hyperparathormonism. The parathyroid hyperplasia encountered in those conditions are frequently of this nature. It must be clearly differentiated from the hyperplasia manifesting a hyperparathormonism. This simple parathyroid hyperplasia corresponds to the simple goitre of the thyroid pathology, in the same manner as primary glandular hyperparathyroidism corresponds to toxic adenoma, and cerebro-pituitary hyperparathyroidism to the Graves' disease of thyroid pathology.

Therapeutics.

Treatment of primary hyperparathyroidism is essentially surgical, consisting in removal of the hypersecreting adenomas. Technique is delicate and has been studied by Mandl, Walton, Churchill and Cope. The adenomas must be located, and as they are sometimes outside the usual parathyroid site this is not always easy. All adenomas must be removed, and this also presents some difficulty as they are easily mistaken for fat or thyroid tissue. Finally some healthy parathyroid tissue must be left so as to avoid severe post-operative hypoparathyroidism. In spite of these difficulties the results of parathyroidectomy are encouraging. Operative mortality is not very high. In Mandl's analysis of 55 parathyroidectomies (1926-1933) four ended fatally.

The ultimate results are good. Bone deformities of course cannot retrocede, and generally renal function is not improved, but the general condition of the patient progresses notably.

Treatment of cerebro-pituitary hyperparathyroidism also is surgical, consisting in removal not of a parathyroid tumour but of parathyroid tissue. The procedure is effective through removal of the hypersecreting tissue and probably also through an obscure mechanism of shock. Accidental removal of thyroid tissue or of fat instead of parathyroid tissue has conferred great benefit, and demonstrates the shock mechanism.

CHAPTER XVI

HYPOPARATHYROIDISM

Hypoparathyroidism is a disease characterised predominantly by a hyposthenic reaction of the parathyroid (more precisely, the parathormone) system.

Tetany, one of the outstanding symptoms of hypoparathyroidism, was first described by Walter Harris in 1689, and later by Clarke in 1815, and Kellie in 1816. In 1852, Lucien Corvisart described it again and named it tetany. Vassale and Generali in 1876 showed the connection between tetany and parathyroid insufficiency. McCallum and Voegtlin in 1908 demonstrated that parathyroid tetany is due to hypocalcæmia.

There is a regrettable confusion between hypoparathyroidism, hypocalcæmia and tetany. " Hypoparathyroidism " is the only precise term indicating a definite disease. Hypocalcæmia and tetany are symptoms met in hypoparathyroidism, but they may also be manifestations of other diseases.

Physiopathology.

Constitutional regulators disturbed. The essential constitutional regulatory disturbance in hypoparathyroidism involves the parathormone system, which is in a state of hypofunction. This is as a rule of primary parathyroid origin, the insufficiency starting at the parathyroid glands. A hypoparathormonism

originating in the diencephalic centre of the parathormone system has recently been demonstrated by the observations of Winer and of Schneider.

Disturbance of a genetic regulator occurs also in hypoparathyroidism. It causes defective reactivity of the various tissues to parathormone. It intervenes in all cases of hypoparathyroidism but sometimes constitutes the essential constitutional disturbance. Here secretion of parathormone is normal but the tissues are insensitive to its action. Certain chronic hypoparathyroidisms are of this origin. They are an application in parathyroid physiopathology of the Seabright-Bantam syndrome (Albright).

Metabolic disturbances determined. The most important are those referring to calcium and phosphorus metabolism. The primary disturbance, according to most authors, is decrease in the excretion of phosphorus, which thus accumulates in the body and particularly in the blood. As the osmotic equilibrium of the blood depends on a special phosphorus-calcium ratio, an excess of phosphorus in the blood means decreased drainage of calcium from its depots, the bones, with resultant calcium impoverishment of the blood and intercellular fluids. Ionised calcium, the only calcium of biological importance, is most affected. Another disturbance of calcium metabolism, more difficult to interpret, is calcification of the brain tissue, noted in some cases (Eaton).

Water metabolism also shows disturbances. The water content of the brain is increased in parathyroid tetany (Baar) and in experimental parathyroprivic tetany (Ellis). This hydration with hypocalcæmia and, principally, other factors causes disturbance in the surface functions of the brain cell membranes, which leads to the building up of abnormal electrical potentials resulting in convulsions. The hydrogen ion concentration of the blood is also disturbed, and alkalosis is noted. This does not depend only on hypocalcæmia.

Protein metabolism also is disturbed in these patients, although the significance of this disturbance is not yet well understood. Protein catabolism is inhibited up to a certain point, and products of imperfect protein metabolism such as histidine and tyrosin are found in the urine.

The outstanding organic repercussion is increase in neuromuscular excitability. It is due to the hypocalcæmia, because the moderating action of calcium on the neuro-muscular system is decreased in this disease through the paucity of calcium. As regards post-operative hypoparathyroidism the hypocalcæmic reaction depends on the difference between the pre-operative and the post-operative levels, not on the absolute level at the time tetany sets in. Thus when the pre-operative level of blood calcium is, *e.g.*, 14 mg. per cent., as in some cases of hyperparathyroidism, a fall to 9 mg. per cent. after operation may determine tetany although the latter figure is in fact normal, but hypocalcæmia is only one of the variables concerned in the symptoms of tetany and of neuromuscular excitability. Other factors intervene.

There are numerous other organic repercussions of the metabolic disturbance set up by hypoparathyroidism, principally loss of weight, disturbances of hair and nail growth, cataract and otosclerosis. The metabolic disturbance of which these are repercussions is not known. Calcium disturbance causes,

besides hypocalcæmia, changes in the ionic equilibrium of the pericellular fluids and thus changes in cellular permeability. Further, the dysfunction of phosphorus and protein metabolism probably contributes to such organic repercussions.

Etiology.

From the clinical etiological point of view there are two great divisions of hypoparathyrodism, parathyroidectomy hypoparathyroidism and spontaneous hypoparathyroidism.

Parathyroidectomy hypoparathyroidism may occur accidentally, the parathyroids being removed in the course of thyroidectomy for goitre. Even nowadays with perfected technique of operation this complication occurs in 3 per cent. of thyroidectomies, because as the parathyroids are embedded in thyroid tissue their removal is unavoidable. In other cases parathyroidectomy is performed for relief of hyperparathyroidism. Cases of hypoparathyroidism following radiotherapy for goitre—a physical parathyroidectomy—also have been reported (de Gennes).

Spontaneous hypoparathyroidism is usually primary glandular, the glandular parathyroid centre of the parathormone system being involved primarily. This occurs through infective factors which set up a parathyroiditis, often (in 58 per cent. of cases) of hæmorrhagic nature. Tuberculosis, syphilis and acute infections are usually responsible. Toxic factors such as fluor in drinking water (Spira) have been incriminated as causing hypoparathyroidism through a similar mechanism, but nothing definite is known on this point. A genogenic factor of inferiority of the parathormone system contributes and explains the familial and hereditary incidence of the disease.

A spontaneous cerebro-pituitary hypoparathyroidism probably exists, the hypoparathormonism originating in the diencephalic centre or the parathormone system. Much is not known about this condition, but it is possible that certain infective factors acting on the diencephalon or certain metabolic disturbances of nutritive origin, causing an abnormal total hyposthenic reaction of the parathormone system, may determine such a condition. It is known that the parathyroids can react with hyperfunction to certain metabolic disturbances, as in rickets for instance and chronic nephritis. Whether a similar mechanism applies to hypoparathyroidism, however, is speculative. Deficient calcium intake or deficient calcium absorption through lack of vitamin D have been suspected as responsible, but these factors are known to cause tetany through the mechanism of direct hypocalcæmia (nutritive hypocalcæmia) without any involvement of the parathormone system.

Symptomatology.

The initial presenting symptom of hypoparathyroidism is usually an attack of tetany. In post-operative cases it appears a few hours after operation. In spontaneous cases it occurs in the course of apparently good health or during an acute disease such as an infection or gastroenteritis.

Less freqently the first syndrome is a visceral spasm. I have seen a case in

which the initial attacks were ascribed to gall-stones. In the course of one attack typical tetany occurred and made possible the diagnosis of hypoparathyroidism, confirmed by disappearance of the cramps with parathormone and calcium treatment.

The complete picture of hypoparathyroidism comprises (*a*) nervous paroxysmal attacks, (*b*) visceral paroxysmal attacks, (*c*) a chronic nervous condition of hyperexcitability, (*d*) a chronic condition of general and local disturbances.

Nervous Paroxysmal Attacks. *The tetanic attack.* This is the most frequent and characteristic paroxysmal syndrome by which hypoparathyroidism is manifested, although it should be remembered that tetany can occur without hypoparathyroidism and hypoparathyroidism without tetany. As a rule hypoparathyroidean tetany occurs with dramatic suddenness. No definite stimulus is apparent, or at most a very slight stimulus. It is marked at onset by a prodromic phase of paræsthesia, tingling and numbness of fingers, toes, lips and other parts of the body and fibrillary twitching, with subjective nervousness, apprehension and restlessness.

Next comes a tonic phase of spasm which is carpal, pedal, facial, and may become generalised into a rigidity simulating tetanus. The carpal spasm is the most characteristic and frequent. The hand contracts in the position of "obstetrical hand," wrist flexed, hand drawn towards the ulnar side, thumb thrust into the palm, fingers slightly flexed at the metacarpophalangeal joint, extended at the phalangeal, and bent over the thumb. In some cases there is acute flexion of the wrist, the hand is drawn towards the ulnar side and the arm flexed across the chest. Intense pain accompanies this contracture, but is not always characteristic and is mistaken for rheumatism.

The pedal and facial spasms follow, although they may occur independently. Both feet contract in the position of equinovarus with strong flexion of the toes. The face assumes an expression of rigidity. The forehead is wrinkled transversely. The mouth is like that of a carp, its corners drawn downwards. Nystagmus, inequality of the pupils are noted, and rigidity of the neck muscles as in a meningeal disease, with which tetany is often confused.

General rigidity, like that of a mild tetanos, terminates this phase in severe cases. A certain degree of pallor is noted during this tonic phase and is due to vascular spasm. Convulsions may follow the period of tonic spasm.

The whole attack lasts from a few minutes to hours in severe untreated cases. The number of attacks varies, but as many as eight per diem have been reported. In untreated cases a status tetanicus comparable to status epilepticus or status eclampticus has been observed.

Formes frustes of tetanic attacks are very frequent but often overlooked because they are atypical and evanescent. The presenting symptom is a tingling of the hands and feet, mild contractions of fingers and toes, and cramps of the muscles of the calves. They occur when the patient is at rest but are aggravated by any physical effort. One of my patients noted simply that driving a car was

terribly strenuous because of frequent spasms in the leg muscles.

Epileptiform attacks. These are rarer and less characteristic of hypoparathyroidism. They may alternate with tetanic attacks or constitute the sole manifestation of the disease. In this last case they give rise to many errors of diagnosis, which can be avoided if in the etiological diagnosis of epilepsy hypoparathyroidism is considered. Hypoparathyroidean epileptic attacks take the form of petit mal or grand mal, and like tetany are provoked by physical exertion, excitation, emotion and febrile diseases. They are explained by the mechanism of vascular spasm induced by hypocalcæmia.

Hypoparathyroidean mental storms are even rarer. The most characteristic are those described after parathyroidectomy, and take the form of a toxic delirium. One of Jeandelize's patients had an attack of alienation with agitation and mutism for eight hours after parathyroidectomy. Another of his patients, also after parathyroidectomy, developed a persecution delirium in which she attacked the physician. Snaper's patient, after the same operation, showed amentia, discontentment, crying spells, night screams, disorientation as to time and surroundings and tetanic attacks. He recovered completely from both tetany and psychosis. Petren's patient showed a peculiar psychic state of irritation and restlessness followed by languor and death 19 days after operation. He had no tetany. These very clear mental paroxysmal attacks of hypoparathyroidism are very important as demonstrating that even a slight variation in the calcium content of the blood can react on behaviour.

Mental attacks have been described in spontaneous hypoparathyroidism, but as it is often difficult to be absolutely certain that such a hypoparathyroidism exists in a patient, these cases are not absolutely characteristic. Shannon has described eight children who developed convulsions followed by mental depression and irrational speech progressing to acute maniacal excitement with screaming, fighting and tearing of clothes. In six cases parathormone afforded great relief. Swanson ascribed a hypoparathyroid origin to certain attacks of sexual hallucination and delusions of persecution.

Attacks of faintness. These are fairly frequent, and are attributed to the intense vagotonia of hypoparathyroidism.

Visceral Paroxysmal Syndromes. These may occur independently or alternate with tetanic attacks. When they occur independently they constitute a difficult diagnostic problem.

Laryngospasm is one of the most common parathyroid visceral spasms and takes the form of laryngismus stridulus. All pharyngo-laryngeal muscles contract and remain spastic, the glottis is narrowed and the vocal cords are held in adduction. Forced respiration ensues with emission of a characteristic crowing sound, retraction of the chest, cyanosis and dyspnœa, and sometimes exophthalmus and coma. In most cases, however, the glottis relaxes after a few minutes, air is heard entering the larynx and cyanosis begins to disappear.

Diaphragmatic spasm may occur independently or accompany laryngismus. It is characterised by an inspiratory apnœa associated with extreme cyanosis. In

Fig. 4
CARPOPEDAL TETANIC ATTACK

rare instances the apnœa is expiratory. It is a very distressing condition and often ends in death.

Bronchial spasm or bronchotetany is met, according to Lederer, in 10 per cent. of cases of severe tetany. It is characterised by marked dyspnœa and tachypnœa associated not infrequently with hyperpyrexia. On physical examination loud bronchial breathing and showers of rales are detected, as well as signs of atelectasis, but it is difficult to diagnose with precision except by X-ray films. Prognosis is invariably bad.

Cardiac spasm or cardiac tetany, described by Ibrahim, is very rare. It may occur like any other visceral spasm in the course of a tetanic attack, or independently. In some cases death is so swift that it is unnoticed by mother or nurse. In others a sudden pallor is followed by apnœa and stoppage of the heart.

Pylorospasm has been demonstrated radiologically in tetany by Falta and Kahn. Ibrahim also upholds the existence of pylorospasm as well as spasm of the rectal sphincter due to hypoparathyroidism. These findings should be borne in mind in the differential diagnosis of attacks of acute abdominal pain.

Chronic Manifestations. *General neuromuscular excitability.* This is an essential feature of hypoparathyroidism and is of course detected independently of the paroxysmal attacks.

The hyperexcitability is detected on the mental side. Intense cerebral activity is apparent. Hypoparathyroidean children are very bright, intelligent and precocious. Association of ideas is rapid and perception so acute that in conversation, in which these children always take an active part, they reply to remarks before the speaker is aware of what he himself had said. Marked mental sensitivity is characteristic, and progresses towards irritability. The hypoparathyroidean reacts violently to opposition and criticism. Mild admonition or fault-finding, even a glance or an attitude, agitates the patient out of proportion to the cause. He reddens with anger, strikes or throws objects at the person who has offended him. This lack of serenity influences the attitude of the patient towards his family, work and social environment—another illustration of the powerful action of a slight disturbance in the internal environment, of a slight deficiency of the blood in calcium or a slight excess of phosphorus, on behaviour and attitude to life.

The same hyperexcitability is detected on the sensorial side. Many visual and auditory stimuli not ordinarily noted by the normal infant are distinct to hypoparathyroideans, and to many such stimuli they react violently. They jump or start violently at a jar or slight noise.

It is, however, on the neuromuscular functions that the hyperexcitability bears most distinctly and is of most diagnostic value. The neuromuscular apparatus is in a state of tension and can be provoked into tetanic or simili-tetanic spasms by stimuli which remain without effect in normal individuals.

Thus constriction of the upper arm (with the cuff of the sphygmomanometer, for example) sufficiently tight to suppress the arterial flow of blood to

the extremities produces typical carpopedal spasm after a few minutes (Trousseau's phenomenon). Tapping the trunk of the facial nerve just in front of the auditory meatus brings about contraction of lips, nose or even the entire side of the face, the response varying from a slight muscular twitching to spasm of the muscles supplied by the facial nerve (Chvostek's sign). There is exaggerated response to galvanic current, as shown by Erb. The peripheral nerves respond to a weaker galvanic current than normally. In children under five years of age cathodal opening of closure with a current under 5 milliamperes determines response, whereas with normal children higher intensities are needed. A parallel but more precise phenomenon is diminution of chronaxy, as elicited by Bourguignon. Prolonged electrical stimulation elicits the myotonic reaction, a very characteristic persistence of contractions after cessation of stimulation.

Other chronic manifestations of hypoparathyroidism. Endocrine diseases being constitutional diseases, their manifestations are widespread, and hypoparathyroidism offers no exception to this rule. It is time to cease considering this disease as synonymous with tetany.

The habitus of these individuals often shows special features. Albright depicts one of his patients as short, rather thick set, very round of face, with index finger longer than the middle finger. Loss of weight and inadequate growth often result from parathyroid hypofunction. The hair is dry and coarse, whitens early in life and falls in patches. The finger nails are soft, and crack and fall easily. They may re-grow, only to fall again. The teeth show disturbance in their growth and calcification, and although more work on human hypoparathyroidean teeth is necessary, it should be remembered that in parathyroidectomised rats opaque spots in the gingival area, defective calcification of dentine and hypoplasia of the enamel have been noted.

The reactivity of hypoparathyroidean children, apart from their nervous hyperexcitability, is disturbed. Transitory febricula has been observed in some cases, indicating that the centre of thermal regulation also seems in a state of irritable weakness. All febrile conditions aggravate hypoparathyroidism. Among foods, milk has been noted to aggravate the disease, probably because although rich in calcium, milk is also rich in phosphorus and thus intensifies the hyperphosphatæmia of the hypoparathyroidean. A clinical counterpart to the increased appetite for calcium shown in parathyroidectomised rats by Richter cannot be demonstrated, because all foods rich in calcium are also rich in phosphorus and therefore noxious in parathyroid insufficiency. It may well be asked, however, whether some cases of plaster-eating among children are not initiated by a need for calcium arising from defective parathyroid function. Sensitivity to adrenalin and pilocarpine is increased through the hyperexcitability of both sections of the vegetative nervous system. Forced breathing soon induces tetanic attacks, as it accentuates alkalosis.

The two outstanding organ manifestations are cataract and otosclerosis, and as they may constitute an oligosymptomatic form of hypoparathyroidism this disease should always be considered in the etiological diagnosis of these

Fig. 5
TROUSSEAU'S SIGN

conditions. Cataract has occurred in hypoparathyroidism following parathyroidectomy, showing the endocrine nature of this disturbance. It has been described also in less distinct cases of spontaneous hypoparathyroidism. The slit lamp now reveals it earlier and more frequently in both forms of parathyroid hypofunction. Otosclerosis has also been described in hypoparathyroidism and reproduced in animals through parathyroidectomy, by Dragstedt and others. Undoubtedly a hypoparathyroidean otosclerosis exists but of course all otoscleroses are not of this origin, and if parathormone has not given good results in all cases this is no argument against an otosclerosis due to this endocrine disturbance. Malherbe has described another form of otopathy, osteospongious otitis, to which he ascribes a hypoparathyroidean origin on the basis of the good effects of parathormone.

Laboratory exploration reveals the metabolic disturbances studied with the physiopathology. Hypocalcæmia and hyperphosphatæmia are outstanding, hypocalciuria and hyperphosphaturia secondary. The total serum calcium is below the normal 9 mg. per cent.; 4–6 mg. per cent. are the figures usually seen. The diminution bears principally on ionised calcium, which is the only calcium of biological significance. Thus, although in certain cases the figures for total calcium may be normal, there may exist hypoparathyroidean hypocalcæmia because the ionised portion of the total calcium is diminished. Hypocalciuria and hyperphosphaturia co-exist but are more difficult to appreciate unless a special diet is followed.

Course of the Disease. Untreated cases of post-operative hypoparathyroidism are essentially chronic. They may show intermissions but terminate through aggravation of symptoms and death in 70 per cent. of cases. The terminal symptoms are cachexia, spasm of glottis, diaphragm and bronchi with asphyxia. In the untreated cases which recover spontaneously (30 per cent.) recovery is due to repair of the trauma of the parathyroids or to hypertrophy of the remaining parathyroid tissue. Treated cases may show complete recovery. Treatment may help to tide the patient over the dangerous phase and nature does the rest. In most cases, however, the cure is only apparent, the patient being maintained in health only through substitutive treatment as are diabetics with insulin, and thus the disease can be considered as lasting throughout life.

Other etiological forms of hypoparathyroidism are less amenable to general description. On the whole they are less severe than post-operative cases.

Special Forms.

Acute forms are not common. Their features are severe symptoms, short duration and fatal termination.

Formes frustes are very frequent. They are characterised by general nervous irritability, signs of latent tetany, tingling of the limbs, flushes of heat, dermographism and atypical or mild spasms. The so-called spasmophilic diathesis of children is often a manifestation of mild hypoparathyroidism.

Oligosymptomatic forms are numerous. They appear in individuals showing a particular localised condition, a " local disease," with the generals and biochemicals of hypoparathyroidism and a special therapeutic response to parathormone and calcium. Hypoparathyroidean epilepsy, hypoparathyroidean chorea (Vassale, Simonini and Tuck), hypoparathyroidean mucomembranous colitis, hypoparathyroidean megacolon, hypoparathyroidean peptic ulcer (Moutier), hypoparathyroidean otosclerosis (Mirvast), hypoparathyroidean spongious otitis (Malherbe), hypoparathyroidean cataract and hypoparathyroidean asthma have all been described.

Absolute proof of the existence of these oligosymptomatic forms cannot be given, and it is neither safe nor helpful to scan every disease for " glands." However, it does appear practical to consider the possibility of a hypoparathyroidean element in epilepsy, chorea, mucomembranous colitis, peptic ulcer, megacolon, otosclerosis, cataract and asthma.

Diagnosis.

The first aspect of the diagnostic problem is diagnosis of hypoparathyroidism without tetany. In the numerous formes frustes manifested simply by nervous irritability and spasmophily it is important not to miss hypoparathyroidism, but conversely one must not forget that these symptoms can arise from non-parathyroid conditions such as nutritive hypocalcæmia and vitamin D deficiency. The same considerations apply to epilepsy, cataract, deafness, etc., which may or may not be of parathyroid origin. It is clear that in all these cases everything depends on detection of the general and biochemical symptoms of hypoparathyroidism. The finding of " latent tetany " is also of great help.

Another aspect of the diagnostic problem is diagnosis of hypoparathyroidism with tetany. First the symptom complex of tetany is differentiated from other convulsive conditions such as epilepsy, tetanus, occupational cramp, tics, habit spasm, myoclonus.

Next the various tetanies not due to hypoparathyroidism must be eliminated. Workman's tetany (housemaid's contraction) is due to an exogenous hypocalcæmia from deficient calcium absorption or nutrition, and is differentiated on the basis of the history of this deficiency. Tetany of cœliac disease or sprue, also due to defective calcium absorption, is differentiated by the concomitant intestinal symptoms and the presence of hypophosphatæmia instead of the hyperphosphatæmia of hypoparathyroidism. Rickets tetany, due to defective calcium absorption from vitamin D deficiency, is differentiated by the concomitant symptoms of rickets. Osteomalacia tetany, which has the same origin, is differentiated by the coincidence of osteomalacic disturbances with hypocalcæmia and hypophosphatæmia. Gastric tetany, due to alkalosis and excessive vomiting, is diagnosed by the concomitant gastric symptoms and the normal values of calcium and phosphorus in the blood. Hyperpnœa tetany and the tetanies encountered in general infections are differentiated on the same basis.

Real hypoparathyroidism, primary or cerebro-pituitary, should be distin-

guished from the parathyroid involvement in Simmonds' disease.

THERAPEUTICS.

Paroxysmal attacks of tetany are treated by intramuscular or intravenous injection of calcium gluconate, 10–20 cc. of a 10 per cent. solution combined with subcutaneous injection of parathormone, 20–100 units according to severity.

The chronic conditions, *i.e.*, the interparoxysmal periods, demands chiefly calcium dihydrotachysterol and, in some cases, vitamin D. Calcium is given orally—injections are unnecessary in such cases, especially as their effect is more transient. Calcium given by mouth raises the blood calcium more slowly than when injected but the effect is more lasting. Calcium chloride has given me the best results in doses of 1·0–2·0 per diem, but the preparation must be reliable as this medicine can cause digestive upsets. Calcium lactate, 1·0–2·0 per diem, or calcium gluconate 3·0–6·0 per diem are more practical agents. They are given in tablets to be chewed, not swallowed whole, or as a powder to be sprinkled on food. Calcium phosphate is contra-indicated because of its higher phosphorus content.

Dihydrotachysterol is the most active therapeutic agent but much more delicate to handle than calcium. It is derived from tachysterol, a chemical fraction of irradiated ergosterol, and is available in the form of a clear oily solution suitable for oral administration. It causes a rise of calcium in the blood more slowly than parathormone, but the effect is sufficiently prolonged to last for days. It thus has cumulative results. It may give rise to intense hypercalcæmia manifested by languor, anorexia, vomiting, headache, stupor, ataxia of the lower extremities, thirst, albuminuria, exanthemes. Administration must therefore be controlled by determination of the blood calcium or by urinary determination with Sulkowitz' reagent. Urine tested with this reagent gives no precipitate if calcæmia is under 8–9 mm. per cent., a white cloud for moderate hypercalcæmia and a milk-like precipitate for a hypercalcæmia threatening complications. The dihydrotachysterol administration advised is 3 c.c. per diem until a white cloud appears in the urine, and after that 1–3 c.c. 3–5 times weekly. It is safer, however, not to rely completely on Sulkowitz' reagent but to resort to blood calcium determination.

Vitamin D, by itself or in the form of cod liver oil, can be given in some cases combined with calcium, but care is necessary as aggravation has been known to follow this medication. According to McLean it acts only in strong doses, 50,000–500,000 I.U. daily, small doses on the contrary causing aggravation. This dosage should of course be supervised. Parathyroid extract by mouth, 0·05–0·10 per diem in combination with calcium is a good adjuvant but only for mild cases. Parathormone is useless in chronic conditions because it may cause too intense a decalcification, and also because it soon ceases to be effective through production of an antihormone. Thyroid can be given in cases with concomitant thyroid insufficiency.

Diet in hypoparathyroidism should be high in calcium and low in phosphorus, but as all foods high in calcium are also high in phosphorus a

practical dietotherapy is based on restriction of calcium-rich foods and addition of medicamentous calcium (by sprinkling it on food, for example). The dietary is thus composed mainly of fruit, vegetables, white of egg, carbohydrates and fats. Foods rich in phosphorus and therefore to be avoided are milk, meat, cheese, yolk of egg, nuts. Individualisation is necessary.

Among physical methods I have found mercury vapour irradiation useful in some mild cases. It can be applied in more advanced cases but with care.

Surgical procedures have been used in some rare cases. Their place in the treatment of hypoparathyroidism has not yet been assessed. Leriche and Jung obtained good results by ablation of the middle cervical ganglion, and ascribe their results to improved vascularisation. Parathyroid transplantation, a more rational procedure, has given good results to Frazier and Tainter. This method can be considered in very severe cases resistant to dihydrotachysterol.

CHAPTER XVII

THYMUS GOITRE

(SIMPLE THYMUS HYPERPLASIA)

Thymus hyperplasia provides an obscure chapter of endocrinology. The term includes both real thymus hyperplasia and absence of thymus involution. Our conceptions can be clarified if we consider thymus hyperplasia as corresponding to the simple thyroid goitre of thyroid pathology. The clinical interest of this condition lies in the pressure syndrome it may determine.

Pressure Thymus.

Pressure thymus stands in the same relation to the thymus as pressure diffuse goitre to the thyroid. It is a pressure " thymus goitre," a hyperplastic thymus causing symptoms by pressing on the important organs contained in the upper outlet of the thorax. Thirty years ago every physician confronted by an infant suffering from dyspnœa, stridor and cyanosis thought at once of hyperplastic pressure thymus. Nowadays the physician in similar circumstances thinks of many other conditions, and many even deny the existence of pressure thymus. Both views are equally exaggerated. The possibility of a pressure thymus cannot be denied because of distinct anatomoclinical facts, but the disease is rare and often diagnosed when it does not really exist.

The cause of thymus hyperplasia and in general of absence of thymic involution is not known. Great discrepancies even exist in the definition of " large thymus," for adequate standard figures of the normal thymus are lacking, particularly as the " normal " thymus varies so much according to age. Thus only definite deviations from the figures of Hammar, given in the description of the thymus, should be considered.

The hyperplastic thymus presses on important organs enclosed in the upper thoracic outlet. This occurs preponderantly in the first, more rarely in the second, year of life, when the thoracic outlet is narrow (two or three centimetres in anteroposterior diameter in the first months of life). Later the

opening enlarges and although theoretically possible, it is exceptional for the thymus to hypertrophy so much as to fill it and exert pressure. The organs affected by thymic pressure in the first years of life are trachea, inferior laryngeal phrenic and cardiac nerves (which may be involved in the hyperplastic tissue), the innominate veins and their collaterals and, exceptionally, the œsophagus.

Pressure from a hyperplastic thymus on the organs of the upper thoracic outlet determines various disturbances. Dyspnœa is predominant, and arises from interference with the trachea and bronchi, as shown by the bronchoscopic exploration of Chevalier Jackson, and more seldom from involvement of the phrenic and cardiac nerves. Change of voice follows from pressure on the same formations and particularly from involvement of the inferior laryngeal. Œdema and venous congestion of the neck result from pressure on the innominate veins and their collaterals. Dysphagia is an exceptional outcome of œsophageal pressure.

Clinic. The predominant manifestations are thymic dyspnœa, thymic death and thymic hypertrophy.

Thymic dyspnœa is the most important manifestation and is due to pressure of the hyperplastic thymus on the trachea, bronchi and cardiorespiratory nerves. It may occur at birth and is then accompanied by cyanosis and necessitates artificial respiration. When of later occurrence it is manifested as a more or less continuous dyspnœa interrupted by paroxysms or as dyspnœic paroxysms. The term "thymic asthma" is applied to these paroxysms, which may be ushered in by a phase of progressive respiratory difficulty or begin suddenly in its full intensity. It is principally an inspiratory dyspnœa with the tragic features that all acute dyspnœas assume in babies. The head is thrown back with marked inspiratory straining. Breathing is difficult and slow, choking the entry of air. Various sounds are heard, the most notable being stridor, which may be inspiratory or expiratory. A brassy crowing cough coincides, hoarseness and aphonia occur, indicating laryngeal involvement. The face is pale or cyanotic, bloated, with marked puffiness and œdema of the eyelids. The neck is enlarged and swollen and its veins, like those of the upper chest, are distended. The child may die during an attack or recuperate gradually.

Thymic death. This is a sudden death occurring without apparent reason or after a slight traumatism, or at the start of a surgical anæsthesia. When met in pressure thymus it is due to pressure on nerves as in the case of Mouriquand and Bernheim. It is, however, more a symptom of status thymicolymphaticus.

Thymic hypertrophy, which completes the pressure thymus triad, is detected clinically by percussion but principally by radiology. Percussion is very unreliable. Radiology is not absolutely reliable, but developments in technique and greater precision in the normal standards would seem to promise more satisfaction from this mode of investigation.

Diagnosis. Except with a dyspnœic attack thymus hyperplasia is difficult to diagnose, since even radiology cannot offer complete certainty. However,

even minor dyspnœic attacks, when detected, are of diagnostic help.

In a severe dyspnœic attack occurring in an infant, pressure thymus is a possible diagnosis, but it is safer to eliminate first the frequent infantile diseases with dyspnœa and then to accept pressure thymus only as a tentative diagnosis.

Therapeutics. Radiotherapy is the method of choice in the exceptional cases when a hyperplastic thymus as yet without symptoms has been diagnosed, and in the more distinct cases with dyspnœa in the interparoxysmal periods. General constitutional methods and particularly ultra-violet irradiation are important.

CHAPTER XVIII

STATUS THYMICOLYMPHATICUS AND MYASTHENIA GRAVIS

STATUS THYMICOLYMPHATICUS

Status thymicolymphaticus has some obscure connection with disturbance of thymus function.

Status thymicolymphaticus has been described by Paltauf in 1889. The clinical picture is clear-cut and often seen but the physiopathology remains obscure. Many authors hold the basic condition to be hypocorticoadrenalism, the thymolymphatic hyperplasia being secondary and the hyposexuality due to the adrenal and not to the thymic disturbance. Others accept a primary disturbance of the thymus and thus of its sex-inhibiting function.

The etiology is unknown. In the days when tuberculosis was seen everywhere a tuberculous infection acting on the adrenal or thymicolymphatic system was considered as a predominant factor. This did not determine the specific tubercular lesions but the common inflammatory reactions (Poncet's tubercular inflammation). This etiology was a favourite at the beginning of this century with French clinicians, who also accepted their other bogey, heredo-syphilis, as a frequent factor.

Nowadays more importance is attached to a genogenic inferiority of the adrenal or thymicolymphatic systems and to nutritional deficiencies. Calcium deficiency is held responsible by some clinicians. The thymus is important in calcium metabolism, and when hypocalcæmia, from defective intake or absorption of calcium occurs the thymus reacts through hyperplasia.

Symptomatology. The eunuchoid triad of special habitus, hyposexuality and eunuchoid psychology is encountered. A special reactivity comprising liability to allergic reactions and thymic death, cardio-arterial hypoplasia and thymicolymphatic hyperplasia gives the special stamp to this disease.

The habitus, with its tallness, macroskelia, narrow thorax and enteroptotic abdomen, is in general lines that of eunuchoidism, but thinness is not notable, thymogenic eunuchoids showing on the contrary a certain infiltration although without obesity. These individuals give the general impression of flabbiness

and pastiness. Their skin is greyish-yellow. In boys the facies has not the dull expression and small traits of hypotestosteronic eunuchoids, but is an "angel-face" intermediate between the infantile and the feminine. The hair is often curly. The other two elements of the eunuchoid triad, hypo-sexuality and special psychology, are those of eunuchoidism in general.

The reactivity manifestations are characterisic. These individuals are prone to allergic reactions such as eczema and urticaria. This fact has an important general significance. To have an allergic constitution an individual must have certain disturbances of his neuro-endocrine system, because this system controls the reticuloendothelial cells, producers of antibodies. The existence of the allergic diathesis in status thymicolymphaticus signifies that the endocrine disturbance at the basis of this condition is a factor of allergic constitution.

The other reactive peculiarities of these subjects are predisposition to sudden death after a slight trauma, a mild infection, an anæsthetic or even without apparent cause. This death may be due to hypocortinism, a vagal crisis (the thymus being vagotonic), pressure of the hyperplastic thymus on important nerves or to a special toxic action of the thymus on the heart demonstrated experimentally by Rowntree and his collaborators.

Cardiovascular hypoplasia is a frequent feature. The heart is small, "en goutte." Pressure is low.

Hypertrophy of the thymus and of the lymphatic system gives the special stamp to the clinical picture. Thymus hypertrophy can be detected only radiologically, and this only with careful technique. Hypertrophy of the lymphatic organs is detected through palpation of the regions in which they normally exist. The lymphatics of the cervical, axillary and inguinal regions are swollen, but neither very hard nor painful. The tonsils are swollen, the spleen is hypertrophied, and lymphocytosis dominates to a greater extent than is normal in children. The hypertrophy of the tonsils is important. It is part of a general disease, not a local condition, although sepsis may supervene. Removal of these tonsils may improve the condition only when they are really infected. Otherwise removal is useless and may even be followed by complications. Otorhinolaryngologists should remember the existence of the status thymicolymphaticus.

Children with status thymicolymphaticus may succumb to an intercurrent infection or to surgical anæsthesia or any other shock. When skilful treatment is given the condition is cured some considerable time after puberty but the individual may remain always hypogonadal and delicate.

Therapeutics. Arsenic, calcium with vitamin D, and phosphorus preparations are the main medicines. Seaside cures and warm sea baths are the best physical agents. Ultra-violet irradiation can be applied but in small suberythematous doses, as many of these children cannot tolerate it. Treatment is thus on a general constitutional basis and is of great value, if started early enough, in preventing the often severe complications resulting from an advanced stage of the disease. The malnutrition reigning in Europe seems to

have increased the number of such cases, and the role of the internist constitutionalist thus gains in importance from the point of view of social medicine.

Myasthenia Gravis

The only distinct hyperthymic condition is that connected with myasthenia gravis. There is a toxic thymoma (corresponding to thyroid toxic adenoma) which according to Murray and McDonald is always associated with myasthenia gravis. In approximately one-half of the autopsy reports on patients with myasthenia gravis benign tumours, hyperplasia or persistence of the thymus have been described. The proportion seems even greater according to recent work, because it is possible that small pathological changes in the thymus have been overlooked. Thymectomy has brought about great improvement in some cases of myasthenia gravis (Blalok and others, Nellen).

It is possible that the diseased thymus produces a substance similar to curare, because the abnormal physiology and pathology of myasthenia gravis present a picture similar to that of curare poisoning.

Endocrinological consideration of myasthenia gravis leads to study of the application of thymectomy.

DISEASES OF THE GONADAL ADRENAL GROUP

CHAPTER XIX

HYPERTESTOSTERONIC ADULT HYPERSEXUALITY

Hypertestosteronic Male Hypersexuality. This is fairly frequent particularly in its mild forms. It is the manifestation of a hyperfunction of the testosterone system beginning at the cerebral centre. It is for the male gonads what Graves' disease is for the thyroid. Its absence from textbooks is surprising, especially as it is of common occurrence.

It is due principally to a genogenic condition of hyperfunction of the testosterone system. Psychogenic and nervous factors, at the opposite pole of those acting in male impotence, are superadded.

When hypertestosteronism begins before puberty an acceleration of development is noted, bearing principally on the sexual characters. The external genitalia develop rapidly. Erections, ejaculations, pubic and axillary hair appear early. Stature also develops rapidly but stops at a certain age because of early closure of the epiphyses caused by excessive testosterone. It is a male pubertas præcox, but essentially different from precocious puberty due to adrenocortical or testicular tumour. Instead of constituting the whole disease, this accelerated puberty is a passing phase and does not show the deformities due to obesity and intense muscularity met in adrenocortical and

testicular tumoral pubertas præcox. It is a more æsthetic pubertas præcox.

When the disease is fully developed examination shows individuals of short stature, short limbs with hypotrichosis of the scalp and hypertrichosis of the body. Their potency is high, with matching libido and fertility.

Psychologically such patients are distinctly extravert and love social and general external activity. Their activity is frequently exaggerated and transformed into restlessness and violence. They are driven by an urge to be constantly engaged in some mental or physical process but their restlessness allows neither of steadfastness nor of any sustained and well-directed effort. Their moods alternate, they show cycloid reactions, and their waves of great elation and activity are followed by phases of depression.

Sexual behaviour disturbances such as active homosexuality are often noted, and are based on the intense sexual drive. When various other factors intervene psychoses may develop. These are of cyclothymic type, and indicate the need for considering the possibility of hypertestosteronism in cyclothymics.

Fancher has described a mechanic, affectionate and obedient as a child, whose character changed during adolescence, when bilateral testicular hypertrophy developed from the twelfth year onwards. He was definitely cyclothymic, his usually normal life being interrupted by paroxysms, waves of irritability and violence. After nine months of detention with the diagnosis of manic depressive psychosis, right orchidectomy was performed with complete relief of symptoms. The testicle was hyperplastic but there was neither inflammation nor neoplasm, and when part of it was grafted upon a eunuchoid patient it induced striking sexual stimulation.

The disease is essentially chronic but after some years sexual depression may follow the hypersthenic phase. The hypersexuality is followed by hyposexuality and the intense activity and restlessness by mental depression.

Therapeutics. General constitutional methods are important (low protein diet, sedative tepid hydrotherapy, psychotherapy). Among medicines various sedatives are useful. Surgery and radiology can be beneficial. Œstrogens can be administered, as in a case of Dunn, in which hyposexuality and marked gynecomastia resulted from 480 mg. of stilbœstrol. Orchidectomy has been performed in one case known to me which showed severe mental disturbances; results were good. Radiotherapy of the anterior pituitary is effective but needs endocrinological supervision.

CHAPTER XX

HYPOTESTOSTERONIC EUNUCHOIDISM

The term eunuchoidism was coined by Griffith to denote a clinical syndrome resembling the condition of eunuchs. Hypotesteronic eunchoidism is a eunuchoidism determined by deficiency of the testosterone system. Three forms can be distinguished.

1. Congenital hypotestosteronic eunuchoidism determined by a genogenic

and thus congenital hypoplasia or even aplasia of the endocrine testis. This form corresponds to Fagge's disease of the thyroid pathology.

2. Acquired cerebro-pituitary hypotestosteronic eunuchoidism determined by an acquired deficiency of the testosterone system beginning at its diencephalic centre. This corresponds to the cerebro-pituitary myxœdema of thyroid pathology.

3. Acquired primary hypotestosteronism determined by an acquired deficiency of the testosterone system localised at its glandular system. This corresponds to the primary myxœdema of thyroid pathology.

Acquired Cerebro-Pituitary Hypotestosteronic Eunuchoidism

Etiology and Physiopathology. This is a eunuchoidism determined by a hypofunction of the testosterone system beginning at its diencephalic centre. The condition is often termed, inadequately, pituitary eunuchoidism. Real pituitary eunuchoidism is caused by hypotestosteronism starting at the pituitary centre of the testosterone system, not at the diencephalic centre. Thus it is due to a lesion or primary disturbance of the pituitary gland, *i.e.*, of the pituitary centre of the testosterone system. Such conditions exist, but enter into the general symptomatology of another disease manifesting this extensive pituitary disturbance, *i.e.*, Simmonds' disease. In cerebro-pituitary eunuchoidism the basic hypotestosteronism originates in a disturbance of the diencephalic centre of the testosterone system. This determines a secondary hyposecretion of β-gonadotropin and consequently hyposecretion of testosterone by the interstitial cells of the testis. Special but obscure factors prevent the reactive gonadotropin hypersecretion which normally occurs after testosterone hyposecretion.

In the genesis of an endocrine-constitutional disease the hormone is not the sole element; the reactivity of the cells receiving it, a reactivity that is genetically determined, plays a certain role. There are even cases of hypotestosteronic eunuchoidism in which testosterone secretion is normal but the cells of the body, particularly those of the genital organs, are insensitive to its action. Such a mechanism has been shown in the experiments on the Seabright-Bantam syndrome. Thus the term hypotestosteronism, like any hypo- or hyperendocrinism, has a certain stamp of relativity.

The thyroxin system also is involved but secondarily to hypotestosteronism.

The general metabolic disturbances consist in (*a*) diminution of the rate of oxidation, thus of basal metabolism, probably a result of the coincident hypothyroxinism, (*b*) intensification of protein catabolism, as testosterone is a protein-anabolic, (*c*) disturbance in creatine metabolism shown by the presence of creatine in the urine, an abnormal phenomenon in males after puberty, (*d*) intensification of fat catabolism, hence thinness except when later a reactive disturbance of the pituitary fat-metabolic hormone causes obesity.

The local metabolic disturbances refer to the cellular components of the male sexual organs, whose metabolism is especially regulated by testosterone. When hypotestosteronism occurs before puberty the genital organs and extra-

genital sexual features of the male develop badly. When this disturbance starts after puberty, *i.e.,* after the male sexual characters have developed fully, the sexual organs and functions retrocede.

Cerebro-pituitary eunuchoidism is determined by various environmental factors acting on a genogenetically inferior testosterone system. These factors, often acting in combination, are of infective, nutritive and psychogenic nature. Infections act through the mechanism of diencephalitis involving the hypothalamic centre of the testosterone system. Nutritive factors are either general malnutrition or particular avitaminoses. General malnutrition, particularly protein starvation, acts by upsetting the whole testosterone system. It seems a very frequent etiological condition, and I have observed in more than three-quarters of the eunuchoids I have seen that severe gastro-intestinal disturbances had occurred in the first two years of life. Eunuchoidism is common among poor populations in the Far East, and undoubtedly the present starvation in Europe is determining many such cases, as seen in various reports. Particular vitamin deficiencies are less obvious in the clinical etiology but experimentation gives a warning of their importance. Besides an etiological role in general malnutrition, the necessity of vitamins E, B and C for normal function of the testosterone system has been shown by experimental work.

Psychogenic factors loom large in the etiology and act on the diencephalic centre of the testosterone system through the cortico-diencephalic connections. Other endocrinisms also act by upsetting the entire testosterone system, beginning at its cerebral centre, either by direct inhibition or by determining an abnormal compensatory reaction. Hyperthyroidism, hypothyroidism, hypoinsulinism, hypocortinism can all enter the etiology. Metabolic disturbances of the mother during pregnancy also must be considered. These are often set up by psychogenic factors. Many of the young eunuchoids I see to-day were born in the days of the financial depression. It will be interesting to note in the future the role of war emotions in the determination of eunuchoidism in war babies. Tumours pressing on the hypothalamus have been noted in the etiology of certain rare cases of eunuchoidism. Notwithstanding its rarity this factor is important for the understanding of the mechanism of production of cerebro-pituitary eunuchoidism.

The Pre-puberal Hypotestosteronic Eunuchoid. Eunuchoids in whom the basic hypotestosteronism has started before puberty show the most complete picture. Their history is one of slow development and principally of pubertas tarda. In the very early years nothing particular is noted, but towards the seventh year the external genitals are seen to be small, and in some cases no testicles can be detected in the scrotum. Later the lagging development of the extra-gonadal sexual characters can be more clearly observed. The external genitals develop slowly. Pubic and axillary hair fail to appear at the normal stage ($14\frac{1}{2}$ for pubic hair, $15\frac{1}{2}$ for axillary). The hair of face and body develop badly, whereas the head shows luxuriant hair. Muscular development is retarded and poor. The mentality remains infantile.

The voice does not break. These boys grow very tall and long-limbed.

When examined at any period of life such patients show the eunuchoid triad of eunuchoid habitus, hyposexuality and special psychology with a whole series of background symptoms.

The eunuchoid habitus. Macroskelic tallness and thinness are the first striking features. Tallness is due to macroskelia or abnormal length of the limbs. The macroskelia is caused by the unchecked action of phyone on the diaphyseo-epiphyseal cartilages, which fail to ossify at the appropriate time as their normal ossification is a function of testosterone. Because of the macroskelia the span is greater than the height and the upper segment (from vertex to pubis) is smaller than the lower (pubis to the soles of the feet). After the twelfth or thirteenth year these measurements should be equal, and this particular anthropometric abnormality is termed " eunuchoid proportions." Thinness is often of a remarkable degree, and is due to under-development of the muscular system and absence of fat. Testosterone is the main regulator of muscular development and to some extent of fat.

The whole habitus is summarised in the words longilinear, asthenic, enteroptotic. The head is small but with great development of the forehead (the so-called " intellectual forehead " is often a hypotestosteronic forehead). The lower part of the face is less developed and the chin recedes. The entire face is thus distinctly triangular, contrasting with the quadrate head and the prominent jaw of the hyperpituitarian. Neck, thorax and abdomen are elongated. The biacromial diameter is relatively small in proportion to the bi-iliac (an intersexual feminine feature). The abdomen is typically enteroptotic and flaccid. The pelvis is wide and flaring (an intersexual feature), the upper thigh showing the convex feminine curve. The hands are abnormally long with very long and slender fingers (artistic hands), and slender wrists free from dorsal padding. The feet also are long, and flat foot is frequent through laxity of ligaments. Cyphosis is constant in distinct cases and is due also to laxity of the ligaments, whose metabolism is regulated in great part by testosterone. The mammæ are sometimes well developed (gynecomastia), the external genitals hypoplastic.

Skin, hair and teeth show distinct developmental disturbances. The skin is soft and velvety, without deep furrows. Its colour is white, sometimes pasty and sallow, due not to anæmia but to the defective melanin content of the epidermal cells. It is dry as a result of defective sebaceous secretion, which is normally promoted by androgens. The same defect accounts for the absence of acne in young eunuchoids.

The hair is maldeveloped on the body but notably abundant on the head (artistic hair). After puberty eunuchoids need frequent hair-cuts but rarely have to shave. The pubic hair ends in a horizontal line as in women. Premature whitening of the hair has been noted.

The teeth decalcify, decay early and severely. They need many stoppings —a point to be borne in mind by dentists, for in such cases the condition is relieved by testicular organotherapy and not by calcium. The hypogonadal

Fig. 6
AN EARLY MALE CEREBRO 'PITUITARY EUNUCHOID. NOTE 'INFANTILE' ASPECT

dental stigma is noted (large central incisors, small lateral incisors, blunt canines).

The whole impression is of a mixture of infantilism and feminism. In many cases feminine features predominate, and such cases I have called morphological male intersexes, morphological androgynoids. They show smooth graceful curves, broad hips, high narrow waistline, absence of bony prominences. They walk with a short, quick tread, often with the swinging step of a woman instead of the long direct stride of man. Many eunuchoids with markedly feminine features give the impression of a certain ambiguous beauty, and were much in vogue for Roman orgies in the days of Nero.

Eunuchoid hyposexuality. This is the second group of manifestations in the eunuchoid triad.

Smallness of the testicles is noted in many cases. This is not an endocrine but a genetic manifestation.

Cryptorchidism also is very frequent. Much has been written lately about this symptom, wrongly described as a " disease." Cryptorchidism may be due to genetic factors as well as to deficiency of β-gonadotropin. When due to the latter cause, as is most frequent in eunuchoidism, it is usually bilateral and of low degree. In its milder forms, the retained testicle lies in the upper end of the scrotum outside the external ring and can be brought into the scrotum by certain procedures of manipulation, change of position and relaxation. There are, in fact, more cases of testis mobile than of true cryptorchidism. In more advanced cases the testes are more permanently in the inguinal canal or the abdomen. Spontaneous descent may occur at any time, principally towards puberty, but is far from constant. The undescended testicles are impaired in their spermatogenic function, which demands certain conditions of temperature encountered only in the scrotum, the intra-inguinal and intra-abdominal temperatures being too high for normal spermatogenesis. Testosterone secretion, however, is not impaired by cryptorchidism although it may be hampered by β-gonadotropin hypofunction, the basis of the cryptorchidism; on the contrary, the interstitial gland may react by hyperplasia. Cryptorchidism due to endocrine factors is amenable to endocrine treatment.

When cryptorchidism is due to genetic factors the picture differs. It is frequently unilateral and may show a more definite ectopic position, the testicle being retained in the upper part of Scarpa's triangle or in the internal aspect of the upper thigh. Spontaneous descent does not occur and endocrine treatment is of no avail.

In male eunuchoidism, although the testicles may descend spontaneously at any time, especially at puberty, there is nothing to indicate the cases in which they will descend and those in which they will be retained permanently. Thus in every case an attempt to promote testicular descent through endocrinotherapy must be made.

Hypoplasia of penis, scrotum, prostate and seminal vesicles, maldevelopment of sexual hair, pubic and axillary, are the most common manifestations of hyposexuality in male eunuchoids. Their precise appreciation is of course

possible only at puberty or after.

Impotence, impaired fertility and lack of libido complete the picture of male eunuchoid hyposexuality. Impotence may be mitigated by the intervention of psychogenic factors acting through the vegetative nervous system but in most cases of pre-puberal eunuchoidism it is intense if not absolute. Impaired fertility is constant in all but mild cases, because testosterone is important in the production and completion of semen as well as in maintaining the normality of the canals through which semen passes. Absence of libido is also mitigated in some cases by psychogenic and neuro-vegetative factors, but is in general absolute. In some cases libido may be ambivalent (an infantile trait) or homosexual of passive form (an intersexual feature).

The eunuchoid psychology. The third element of the eunuchoid triad. The mental syndrome of male eunuchoids depends largely on the deficiency of the male maturation function which testosterone normally promotes through the psychoassociational cortex, but also on various purely psychogenic factors, such as the attitude of the patient to his deficiency, depending on constitutional personality traits.

Introversion is marked. In mild cases it is manifested by mere shyness. At school it is noted that these boys like to stay alone and read, and do not indulge in competitive sports. In more serious conditions there is lack of emotional tone, a tendency to day-dreaming and a life confined within the self. The personality is schizoid, and these individuals, when certain other factors intervene, react later with schizophrenic manifestations.

Emotivity and its corollary anxiety often dominate the picture. This is an intersexual feminine feature. These patients resemble women in that the emotional element is uppermost. Feminine mannerisms are often observed, cases of male hysteria falling within this category.

The intellect of eunuchoids is good. If they are retarded at school this is due more to emotional factors. Their intellect, however, is more of feminine imitative than of male creative type. Such individuals tend to practise the arts, especially music, literature and ballet dancing, rather than the sciences. However, even in the arts they never attain creative proficiency.

Psychotic reaction types develop in some cases on the basis of a special predisposition fostered by other non-endocrine factors. Hypotestosteronism contributes to the reaction pattern of these psychoses, which are usually of schizophrenic type.

Background symptoms. Eunuchoid habitus, hyposexuality and the special psychology are the leading syndromes of this disease, but many other symptoms form a background to the clinical picture.

The reactivity of these patients offers special features. Asthenia is common and continuous. They wake up tired and feel tired throughout the day. All their symptoms are aggravated by physical exertion, and in some cases there is severe incapacity. They like to stay at home and read, avoiding sports and physical effort. Hyperthermic reactions occur in the form of chronic febricula or fever but less frequently than in female eunuchoidism. Susceptibility to

infections, particularly to colds, is notable, as also to peptic ulcer—Draper's ulcer habitus is a hypogonadal habitus. I do not believe in a special susceptibility to tuberculosis, and ascribe this opinion to misdiagnosis of many eunuchoids, with their asthenia, leanness, digestive upsets and febricula, as tuberculous.

The voice remains high-pitched after puberty instead of changing to the adult male range. It is either soprano or, in some less marked cases, becomes tenor, but never reaches virile baritone or bass. For the understanding of this feature it should be remembered that before puberty the normal voice for all humans is soprano. At puberty and afterwards the laryngeal cartilages develop, but less in woman than in man. Woman keeps the infantile soprano, man passes through the stage of tenor to a virile baritone or bass. According to the degree of hypo-orchidism the voice stays at soprano or tenor, the latter representing a higher degree of masculinisation, but not complete masculinisation. In women who virilise, on the other hand, the voice assumes a contralto, deep baritone or even bass timbre, as evident in some adrenal hypercortinisms of the climacteric and typified by the baritone of the virago mother-in-law.

Digestive upsets are frequent. They are attributed to gastroenteroptosis, but this is itself a result of hypotestosteronism. Tachycardia is noted but less often than in female eunuchoids.

Laboratory investigations, in spite of much work, have not yielded important signs. Androgens and œstrogens have been found diminished, normal or increased, although diminution is most frequent. Until it is possible to differentiate the various androgens found in the urine, such determination is of small clinical importance. Pituitary folliculostimulin (*a*-gonadotropin) is not increased in the urine of eunuchoids as it is in eunuchs.

The basal metabolism is low as a result of defective thyroid function secondary to hypotestosteronism. Creatine may occur in the urine after puberty, *i.e.*, at a time when it should not be present, and creatinine is more abundant than normally.

The Post-puberal Hypotestosteronic Eunuchoid. When hypotestosteronism occurs after puberty and the eunuchoidism is therefore tardive, the clinical picture shows a different individual. Morphologically tallness and eunuchoid proportions are absent. Thinness may exist, but usually obesity sets in early and may attain high degree. The skin soon assumes gerodermic features through a secondary hypothyroidism. The hair of face and body shows regressive changes and the scalp hair may whiten prematurely. Acromegalic changes due to reaction of the phyone system may be noted.

The genital organs and functions retrocede. Penis, scrotum and testicles shrink. Libido and potency wane.

The general activities dwindle, and some degree of mental depression sets in.

Many such cases have been described as Rummo and Ferranini's syndrome or as regressive infantilism (Gandy). These terms should disappear from nosography. They complicate unnecessarily a simple chapter in the natural history of eunuchoidism.

Therapeutics. General constitutional methods come first into consideration. Hygiene, fresh air and exercise must be regulated. The tendency of young hypotestosteronics to avoid sports should be counteracted. Psychotherapeutic leadership and encouragement must be exerted and strenuous efforts must be made to relieve the patient of his inferiority complex and inspire him with confidence. Diet must be rich in proteins and adequate in vitamins and minerals. Of physical methods, ultra-violet irradiation and bracing climates are the most effective. Certain constitutional medicines such as arsenic, iron, phosphorus, laxatives and sedatives are applied according to the individual indications.

Chorionic gonadotropin, an interstitial cell stimulant, is the basis of endocrinotherapy. Twelve injections of 500 R.U. each, are given first, twice weekly, and later similar courses are repeated according to individual indications. Testosterone propionate is a useful adjuvant but only in small doses, and preferably orally in the form of methyl testosterone, as strong doses depress the gonadotropic secretion of the antepituitary. A more intensive testosterone treatment should be applied, however with care, in cases where it is necessary to stop an abnormal statural growth. In such cases I use pineal gland in addition. Other adjuvants are pregnant mare gonadotropin, adrenal cortex, thyroid and sometimes thymus, applied according to the usual clinical empirical technique.

This major endocrinotherapy should be used only in definite and severe cases. The physician must beware, particularly in boys, of the psychological trauma of injection treatments. In most cases treatments should be limited to general constitutional measures and oral preparations. I often use the following combination for oral treatment.

Thyroid	0·02
Adrenal cortex	0·05
Anterior pituitary	0·15
Testis	0·15

This is made into capsules, of which two are taken daily in alternate weeks. The dosage of the various components varies according to individual indications.

Especial mention should be made of eunuchoidism with cryptorchidism. Much ink has flowed on the subject of the hormonal treatment of " cryptorchidism," and the discussion will not cease until it is recognised that cryptorchidism is not a disease but a symptom of various diseases. To attempt to treat cryptorchidism due to developmental defects by means of chorionic gonadotropin is to court failure. However, when cryptorchidism is a manifestation of eunuchoidism treatment in general (not only hormonal administration) also helps the testicle to descend. The most delicate point arises in those cases in which cryptorchidism is an oligosymptomatic form of hypotestosteronism. Here chorionic gonadotropin is administered after the age of nine and in fairly large doses, but under careful supervision. Treatment should

Fig. 7
MALE CEREBROPITUITARY EUNUCHOIDISM IN AN ADULT. (THE SO-CALLED TARDIVE EUNUCHOIDISM). NOTE 'FEMININE' ASPECT

be short and intensive, never prolonged. If after two months of intensive treatment the testicle shows no tendency to descend, hormones should be abandoned and recourse to surgery is necessary.

PRIMARY TESTICULAR HYPOTESTOSTERONIC EUNUCHOIDISM (ACQUIRED).

This eunuchoidism is determined by hypotestosteronism originating in the testicular secretory centre of the testosterone system.

Genogenic inferiority of the testicle is a basic condition or predisposition. Various environmental factors act on the genogenically inferior testicular glands. Infections are important and act through the mechanism of infective orchitis. Mumps, orchitis, syphilitic, tuberculous and gonococcic orchitis are prominent. As I have pointed out with Sourdel, this orchitis may be latent for a very long time as far as the production of eunuchoidism is concerned, through compensation by other endocrines, mainly the thyroid. When for any reason such compensation fails, eunuchoidism occurs. Many cases of so-called tardive eunuchoidism are explained through this mechanism. Toxic factors such as alcoholism, morphinism, plumbism and nicotinism may cause a primary testicular eunuchoidism by producing a toxic orchitis which in other respects is clinically latent. Nutritive factors of general malnutrition or deficiencies of particular vitamins such as B and E also may act directly by impairing the nutrition of the testicle.

The clinical history of these patients, except for certain features in their etiological constellation, resembles that of cerebro-pituitary eunuchoidism. The picture, however, is less complete. Therapeutic handling is similar, but testosterone acquires greater importance.

CONGENITAL HYPOTESTOSTERONIC EUNUCHOIDISM.

This disease is to the testicle what Fagge's disease or congenital hypothyroidism is to the thyroid. Its physiopathological basis is a genogenic testicular defect reaching hypoplasia and even complete aplasia, that is, absence of testicles. Such congenital anomalies are rare but have been describd. Hypoplasia is more frequent.

The clinical syndrome is one of severe eunuchoidism or eunuchism. It is in fact a congenital castration. As it is a genogenic disease it is often familial. Furno has studied a family of congenital castrates and has described five cases in three generations. In his cases trophic disturbances of the ligaments giving rise to cyphosis were noted besides the severe eunuchoid syndrome.

The habitus of these individuals is not always that of the typical eunuchoid. Some of them may be microsomic, even dwarfs. This is due to intervention of other genetic anomalies.

Congenital hypotestosteronic eunuchoidism is not synonymous with congenital hypo-orchidism. In fact, congenital hypo-orchidism may exist in the physiopathological picture of other diseases, particularly of certain deep constitutional male intersexualities. The clinical picture should always have priority in disease differentiation.

The basis of treatment is testosterone.

CHAPTER XXI

MALE EUNUCHISM

Male eunuchism is a complete testicular failure due to castration. It offers definite characteristic peculiarities. The Greek term εὐνούχος stands for εὐνὴ ἔχω, the guardian of the nuptial bed, because of the special functions assigned to eunuchs by the ancient barbarians of the East. Eunuchism is complete or incomplete according to the removal of one or both testes.

Eunuchism has been studied scientifically in many modern works. One of the best studies comes from Zambaco, a Greek physician of Constantinople and physician to Abdul Hamid. His work was based mainly on eunuchs of the Moslem world. Matignon and more recently McCullagh studied the eunuchs of Imperial China. The most important studies, however, refer to the Skoptic eunuchs. Pelikan, a leading Russian physician, made the first studies in 1876, but it is only during the last thirty years that precise anthropological and clinical methods have been applied, by Tandler and Grosz (1909), W. Koch (1901) and Eugene Pittard, professor of anthropology at the University of Geneva, who in 1934 published an important work on the subject.

Male castration has been performed from very ancient times, although its scientific study is very recent. Herodotos attributes the introduction of this mutilation to the Assyrians. It has been practised in order to obtain servants for the women of the great, guardians of the harems, it has been performed as a crime, and for religious reasons, for the purpose of achieving male soprano voices, and also for therapeutic reasons.

Castration for the purpose of obtaining guardians of women, originating from very ancient times, has disappeared nowadays. The last eunuchs of this origin were those of the Moslem world and of Imperial China up to the first years of this century. Castration as a crime, including punishment of an enemy, was another ancient procedure, one of the most dramatic criminal castrations being that of the great philosopher Abelard at the instigation of the uncle of the seduced Heloïse. Castration for religious reasons is of similarly ancient origin. The young priests who consecrated themselves to the cult of Diana of Ephesos were castrated, and some of those devoted to the cult of Cybele underwent this mutilation, including the Roman Emperor Heliogabalus who was thereby enabled to become chief of the priests of Cybele when the cult of this goddess was introduced into Rome. Some of the early Christians submitted to castration so as to remove the temptations of the flesh, the most brilliant example being Origenes. Some of the first patriarchs of Constantinople became eunuchs, and in 325 the Council of Nicæa decreed excommunication for castrates save for those mutilated by the enemy or for medical reasons. In the third century there was a sect of Christian castrates, the Velesans. There exists to-day a sect in Rumania and Russia, the Skoptzys, who practise castration for the same religious reason, and are famous for

medical reasons because on them is based the latest work on eunuchism. Castration was also performed in the sixteenth, seventeenth and late into the eighteenth centuries to obtain singers with "angelic" soprano voices. The castrates of the Sistine Chapel choir were famous. To evade the interdiction of the Council of Nicæa the church accepted that these boys were castrated for medical reasons. Finally, there is castration for medical reasons, which include castration, often accidental, by X-rays and traumatic castration.

The Pre-puberal Castrate. When castration precedes puberty the clinical picture resembles that of pre-puberal eunuchoidism, of which it is an exaggerated and somewhat modified form. In broad outline the same eunuchoid triad of eunuchoid habitus, hyposexuality and special psychology and similar background symptoms are noted, but with certain distinctions.

The eunuchoid habitus is similar to that described for eunuchoidism. The only difference is that the scalp hair does not grow grey prematurely, and the tendency to dental caries is much less marked. The subsequent development of this habitus also shows certain differential features. Obesity often develops early and is helped by the alimentary excesses in which eunuchs indulge in their search to compensate their lack of the pleasures of Aphrodite by an abundance of those of Bacchus. The skin also is more notably gerodermic. The most distinct feature, however, is development of an acromegalic syndrome due to an abnormal reaction of the phyone system. This explains the acromegalic eunuch.

The hyposexuality resembles that of eunuchoidism but is much more accentuated.

The psychology, although in broad outline similar to that of eunuchoidism, offers certain special features due to personality traits. Many of these are unconnected with the mutilation, such as the fanatical religious traits of the Skoptzys. Of more distinct endocrine origin are the feminine mannerisms, the intense sensitivity and the introversion met in castrates.

Other personality traits depend on the psychological reactions of castrates to their mutilation. These vary as much as those of normal persons to various difficulties of life. Lying, cunning and absence of moral scruples may be a psychological reaction in some Oriental harem eunuchs, for instance, but is not evident in religious castrates. On the whole, however, eunuchs are lazy and apathetic, their intellect is poor with certain notable exceptions and in point of fact Pittard, applying the Manouvrier method, found a distinctly diminished cranial capacity.

The background symptoms of the eunuch show no particular feature except for flushes of heat resembling those of the menopause occurring particularly in surgical castrates very soon after the operation. They represent a nervous vegetative vagotonic or a thyroxin reaction.

Biochemically there is nothing very definite. The basal metabolism is low through a secondary thyroid depression. The pre-puberal creatine persists in post-puberal life. Androgens are diminished, although not constantly.

Up to this point the biochemical findings are similar to those of eunuchoidism. The outstanding feature, however, and one not found in eunuchoidism, is an excess of *a*-gonadotropin (F.S.H.) in the urine.

Life is not shortened in pre-puberal eunuchs. Unlike eunuchoids, they are not fragile vessels, and live long. In many cases, however, development is complicated by behaviour disturbances reaching the degree of psychosis.

The Post-puberal Castrate. When castration occurs after puberty the eunuchoid macroskelic tallness is lacking, but the penis shrinks, the prostate remains small and the hair of head and face diminishes. This is not constant, however, and Pittard distinguishes pre-puberal from post-puberal Skoptzys by the terms Skoptzy glabre (pre-puberal) and Skoptzy poilu (post-puberal). The illustrations in his book are very characteristic. Hip obesity with adiposomastia or gynecomastia develops, sometimes rapidly and intensively.

Post-puberal castrates are characterised essentially, however, by their sexual syndrome, which differentiates them not only from pre-puberal castrates but also from pre- and post-puberal eunuchoids. Potency and libido persist very frequently. This is not astonishing, because potency and libido depend not only on testosterone but also on other hormones, principally pituitary gonadotropin, and on the nervous system. Kolle has reported that of 58 surgically castrated males, one-third preserved their potency and libido. McCartney found gonorrhœa in 10 of the 23 eunuchs he examined. Osman and Shanklin, and Lange, have reported similar observations.

An observation by Rowe is very characteristic. A man was castrated for surgical reasons at the age of 25. Though previously energetic and widely travelled he became an unambitious and lethargic person, and took no interest in women. Nine years after castration he fell in love with a young woman, married her and not only recovered libido and potency so that sexual intercourse took place with entire satisfaction to both parties, but his outlook on life was revivified and he started a new and successful business venture.

In eunuchism the retention of sexual power depends to a great extent on the subject's pre-operative male characteristics, type of personality pattern and tendency either to resign himself passively to his sexual defect or to fight and endeavour to compensate it.

The course of the disease offers no peculiarity.

Therapeutics. A short time ago I was consulted by a young man who had been castrated for surgical reasons at the age of two. He had lived a normal and active life, had a good career, had indulged in sports, and although not potent had enjoyed life with women. He was rejected for military service, however, and although he tried to compensate his feeling of duty by helping in the air defence of his much-bombed home town, his outlook had changed and he was tired, depressed and melancholy. This shows our wrong attitude to castrates, and those who frame military regulations might well recall that one of the greatest generals of the ages, Narses, was a castrate.

Eunuchism need not be a tragedy. It does not involve diminished vital capacity, as does eunuchoidism. Many eunuchs have been outstanding in their careers. The whole problem lies in the direction of these individuals, hence the predominant role of psychotherapy. Although general constitutional measures form the basic procedure, endocrinotherapy is as indispensable as it is for diabetes. It cannot be summarised, however, in the term " replacement treatment." In the first place, for psychological reasons the oral administration of methyl testosterone is preferable. Furthermore, it should be given in courses with intervals of rest. Finally, in some circumstances it needs to be intensified when the internist considers this necessary. Such circumstances arise when it is desired to tide the patient over bad phases by restoring his potency or general virility, even temporarily, when it is necessary to give him confidence and reinforce the psychotherapeutic handling. Injections or pellet implantation can take the place of oral administration, or even testicular grafts with their powerful psychotherapeutic accompaniment. All this must be done on the basis of accurate clinical observation and with the adroitness born of experience. Medicine is an Art, and notwithstanding the help of Science it will always remain an Art.

CHAPTER XXII

MALE CLIMACTERIC DISEASE

Physiopathology and Etiology. The climacteric is a normal phase of life. It is the opposite of puberty and indicates the involution of the gonads. Normally this involution is compensated by appropriate action of the other endocrines and the other elements of the system of constitutional regulation, and thus the climacteric is silent. When such compensation is lacking, however, disturbances occur, the climacteric is abnormal, and climacteric disease arises. This occurs in men as well as in women, and to deny the climacteric of men is a negation of biological principles.

The physiopathology of male climacteric disease is similar to that of its female counterpart. Here also the basic involutional hypogonadism and the abnormal neuro-hormonal and psychological eompensatory reactions must be considered. The basic involutional hypo-orchidism determines, besides progressive diminution of potency and libido, prostatic hypertrophy, which, according to T. E. Paul, is thus a manifestation of male climacteric disease. This is debated, but there seems some truth in the conception of Lacassagne and Zuckermann, according to which the prostatic hypertrophy involves the female vestigial formations of the prostate under the influence of the œstrin normally present in the male, which no longer undergoes the antagonistic action of testosterone. The abnormal reactions of the other neuro-hormonal systems also are similar to those occurring in women.

Of the metabolic disturbances arising from these abnormal reactions one of the most interesting bears on cholesterol metabolism and results in athero-

sclerotic manifestations. The sterols play a great role in human life. The hormone of the "organiser" (the centre in the early embryo which directs tissue and organ differentiation in the developing embryo) is a sterol, as shown by the brilliant work of J. and D. M. Needham and of C. Waddington. When this organising sterol becomes unnecessary and the organised being grows, another sterol intervenes, growth vitamin D. When growth ceases and the growth sterol becomes unnecessary other sterols dominate the processes of the body, the sex hormones. And when in their turn the sexual sterols have outlived their utility, atherosclerosis and cancer appear. In atherosclerosis cholesterol is known to play an important role, and cancerigenic substances have been demonstrated by C. P. Dodds as of sterolic constitution.

As in women, the climacteric disease of men is caused by factors bringing an early and intense hypogonadism and an abnormal reaction of various neuro-hormonal systems and of the psyche. Among factors causing early and intense hypogonadism exhaustion due to a late marriage is potent. One must admire the intuition of Napoleon's physician Corvisart, who on medical grounds advised his master against the marriage with Marie Louise. His counsel was disregarded, and soon afterwards the downfall of Napoleon started as a result of various disturbances inherent in the neuro-endocrine elements of the climacteric disease. Predominant conditions making for deficiencies of other neuro-hormonal systems and of psyche are mental strain, grief and anxiety. These are more serious agents in older persons, who have fewer sources of compensation, than in the young whose thought and activities are trained on a goal, fame or fortune and who are therefore less vulnerable. In contrast to women, however, men do not suffer acute psychological trauma from the gradual wane of sexual potency and libido. Sex is not the centre of life for them, whereas women see by the menopausis that their sexual life is at an end and feel that living itself is empty. Men, however, may experience fear of the advancing years, dread of chronic invalidism, of economic dependance, of loss of position or dominance in the family or profession. On balance, the extravert activities of man aimed at the acquisition of power and riches, and absence of a strident signal like the menopausis to mark the cessation of sexual activity, confer on him a relative psychic resistance and make male climacteric disease a less common and a less clamorous condition than its female counterpart.

It is difficult to assess the time of the climacteric in men, as the involutional hypogonadism is very slow in its development and there are great racial and individual variations. It can be roughly placed in the late fifties, later than in women, and thus climacteric disease, in which involution takes place earlier, occurs in the fifties or sixties.

Clinical History. Morphologically, obesity is common, although thinness may occur in some cases. The obesity is usually due to an abnormal compensation from the lipoitrin system and is of pituitary type (middle-aged spread). It may, however, be due in some cases to an abnormal compensation from the cortical system and show the features of adrenal plethoric obesity.

From the sexual point of view libido and potency wane progressively through the primary hypotestosteronism. Fertility dwindles and disappears for the same reason. These are normal climacteric manifestations and are not part of climacteric disease except when they establish themselves rapidly and in severe form. It is difficult to distinguish the normal climacteric diminution of libido, potency and fertility from that due to climacteric disease in the absence of precise data on the normal cessation of these functions in man, individual variations being numerous and striking. Each case must be judged on its own data, as the distinction remains important because whereas treatment of the sexual symptoms is justified when they are due to climacteric *disease* the general health of the individual is endangered by treatment if they are part of the normal ageing process. No conscientious physician would induce re-erotisation.

In some cases the onset of the disease is marked by intensification of libido and potency as an abnormal compensation from the pituitary gonadotropic system and the psyche. Disturbances of behaviour, sexual frivolities, are the result and constitute the " démon du midi," an inelegant swan-song of sexual life. Libido may take a homosexual direction through arteriosclerotic lesions of the brain.

Prostatic hypertrophy is a striking sexual manifestation of the male climacterium and is attributed to unchecked œstrin action. It constitutes the most frequent oligosymptomatic form of male climacteric disease.

The reactivity manifestations are dominated by a marked asthenia. This may even be the first presenting symptom, driving the patient to seek advice for an unusual and inexplicable feeling of fatigue or inability to work. Chilliness with lack of perspiration is frequent and due to a reactive hypothyroidism. In rarer cases, where the adrenocortical reaction dominates, activity is intensified. The flushes of heat so characteristic of female climacteric disease do not occur.

Mental disturbances, which often colour the whole picture, arise from an interplay of endocrine metabolic and psychogenic factors and take the forms of emotivity, irritability, anxiety, restlessness and depression. In predisposed individuals real psychoses of depressive type (involutional melancholia) develop.

Male climacteric disease often crystallises into prominent cardiovascular manifestations resulting from an abnormal adrenal compensatory reaction. They consist in hyperpiesia, atherosclerotic symptoms and neurocirculatory asthenia. The connection of these " diseases of the fifties " with the metabolic disturbances set up by the climacterium is one of the most notable advances of recent years, and the cardiologist of constitutional outlook can do much for these patients by treating their basic condition, male climacteric disease. Constipation is another organ manifestation frequent in this disease. It is of atonic type, evacuation requiring much straining, and reacts heavily on the mental condition of these patients, in whom it develops a hypochondriac anxiety about their stools. Cephalalgia and polyuria also are noted.

The biochemical symptoms frequently include an increase of urinary folliculostimulin (*a*-gonadotropin). Androgens are usually diminished and œstrogens are present in the urine (although absent from that of elderly women). The hormonal syndrome, however, offers nothing definite or characteristic. The metabolic findings depend on the various reactive endocrinisms.

The course of the disease varies. Usually the first general manifestations of endocrine imbalance are followed by a state of endocrine equilibrium, a phase of calm which ushers in old age. As Halford wrote: "When the powers of the constitution are superior to the influence of the malady the patient loses his symptoms gradually, recovers his rest and his appetite and, to a certain degree, his muscular strength and flesh; but the energies of the frame are never again what they were before nor does the countenance recover its former volume and expression." When climacteric disease has crystallised into a cardiovascular manifestation the course of the disease depends on that disturbance.

Therapeutics. As in female climacteric disease, general constitutional methods claim first consideration. Appropriate hygienic measures, nutrition, certain non-instrumental physical procedures, and medicines correcting the general disturbance of the constitution are used. Testosterone administration, however, forms the basis of treatment and has changed the outlook of such patients. It palliates the nervous manifestations, gives back strength and energy, arrests prostatic hypertrophy up to a certain point, and in particular has a remarkable effect on the cardiovascular manifestations. As individuals with male climacteric disease principally consult cardiologists, the latter should look actively for that constitutional basis of many anginal, atherosclerotic and hyperpiesic manifestations. Brilliant results from testosterone have been reported lately in such cases.

Testosterone treatment is delicate, however, and demands the strictest application of the clinical empirical method, that mainstay of the practice of constitutional medicine and endocrinology. The aim is to restore the constitutional balance deranged by testosterone deficiency, but an excess of testosterone introduced therapeutically may upset the balance in the other direction. Re-erotisation in particular is a danger signal, and the pleasure of the patient when this occurs should not blind his physician to the red light.

Steinach's operation is not always successful, although it is said that certain prominent Viennese scientists have been brought back to an active life by this procedure. According to Steinach the operation he has proposed—ligation of the spermatic duct—stimulates interstitial gland function. However, much remains to be done to clarify the experimental basis of this operation, and a psychogenic factor of suggestion cannot be rejected.

The testicular grafts so clamorously advertised by Voronoff can be ignored. Their action is that of a strong injection of testosterone, although there probably coincides an influence of absorbed modified protein, thus a proteinotherapeutic addition. They have a powerful suggestive effect which causes harmful re-erotisation, and in fact many individuals who have undergone this

operation have died after a brilliant swan song.

Treatment of male climacteric disease must be clearly distinguished from rejuvenation, *i.e.,* re-erotisation. Climacteric disease is an endocrine-constitutional disease. It is a rupture in the balance of the constitutional regulatory system originating in involutional hypo-orchidism. It is a complex of psychological, cardiovascular and other disturbances arising from an abnormal reaction of psyche and various neuro-hormonal systems to the involutional hypo-orchidism, and treatment aims at restoring that balance. One of the elements of treatment is administration of male hormone to compensate the hypo-orchidism and thus enable the psyche and neuro-hormonal systems to attain the balance normal at the particular age of the patient.

Rejuvenation, signifying re-erotisation, is a completely different matter. Ageing is a deep constitutional process involving simultaneously the whole substance of the body. Testicular involution is only one element of senile involution, not the cause of this involution. Man does not become old because his testicles involute; his testicles involute because he grows old. It is therefore unbiological to attempt to palliate the normal senile involution of sexual function and also dangerous, because the entire body is tuned at an involutional level and re-erotisation upsets the balance. For this reason attempts at re-erotisation by means of testicular grafts have often failed with tragical consequences. Treatment of male climacteric disease aims at restoration of neuro-hormonal and physical balance, not at attaining a sexual function unnatural for the age. It is true that these processes are separatd only thinly, but for this very reason we must proceed carefully.

CHAPTER XXIII

HYPO-ŒSTRINIC EUNUCHOIDISM

(FEMALE EUNUCHOIDISM)

It was Theophile de Bordeu, I believe, who first mentioned female eunuchs, comparing the condition resulting from female gonadal deficiencies to that of male castrates.

Cerebro-pituitary Hypo-œstrinic Eunuchoidism

This is determined by a deficiency of the œstrin system beginning at the diencephalon. It is often described erroneously as " pituitary eunuchoidism," but primary pituitary disturbances determine a more complicated disease (Simmonds' disease) showing certain traits of eunuchoidism as part of a more complex clinical and physiopathological picture. Pituitary lesions can never be so localised as to determine a pure hypo-œstrinism.

Œstrin regulates the metabolism and thus the development of the extra-gonadal (the so-called secondary and tertiary) sexual characters. Its deficiency, when occurring early in life, causes imperfect and retarded development of these characters. Furthermore, œstrin promotes ossification of the diaphyso-

epiphyseal cartilages, and its deficiency therefore allows these cartilages to remain open too long and to continue developing under the action of pituitary growth hormone which, being antagonistic to folliculostimulin, is secreted superabundantly. Unlike its male counterpart, hypotestosteronism, hypo-œstrinism shows no intersexualisation (virilisation). Although the male hormone exists normally in women its action, even when unchecked by œstrin, does not lead to virilisation.

Another class of manifestations results from an abnormal reaction of the other neuro-endocrine systems in their endeavour to compensate the metabolic disturbances set up by the hypo-œstrinism. Abnormal reaction of the posterior pituitary system results in pituitary obesity. Abnormal reaction of the pituitary growth system leads to acromegaloid or gigantic changes. Hyper- or hypo-thyroidism occurs through abnormal reaction of the thyroid system. Hyper-piesia and a special obesity result from abnormal reaction of the adrenal system.

Cerebro-pituitary eunuchoidism arises from an interplay of genogenic factors of inferiority of the œstrin system and various environmental factors. The genogenic inferiority is demonstrated by the familial and hereditary relations of the disease. The environmental factors are nutritive, infective, toxic and psychogenic. The nutritive factors are very important in this form. General malnutrition upsets the whole œstrin system, and is often found in the history of female eunuchoids. Particular avitaminoses probably act by removing from the body factors necessary for normal œstrin function. Vitamin B seems necessary for œstrin function, vitamin E for the progestin system. Infective factors act in the cerebro-pituitary form through their localisation in the diencephalon. Psychogenic factors, acting through the mechanism of cortico-diencephalic connection on the diencephalic centre of the œstrin system, are considered important nowadays. As in nearly all endocrine diseases, all these etiological conditions may act in combination in various proportions, constituting for each patient an individual etiological constellation.

In rare cases cerebro-pituitary eunuchoidism results from a tumour pressing on the hypothalamus.

The Pre-puberal Hypo-oestrinic Eunuchoid. In some cases œstrin disturbances occur early, usually before puberty. Onset is slow, symptoms developing progressively. Patients usually consult for menstrual disturbances. In some cases difficult development, digestive upsets and nervousness are the presenting symptoms for which these patients seek relief.

The girl grows rapidly and becomes long-limbed. The breasts fail to develop towards puberty. Axillary and pubic hair do not appear at their usual time. Menstruation does not occur at the normal age (11–13 in temperate zones). Certain infantile mental and emotional traits persist. Puberty is thus retarded, and the girl does not mature.

The Eunuchoid Triad. The same eunuchoid triad of eunuchoid habitus, hyposexuality and special psychology appear as in male eunuchoidism. There are differential features, however, due to particular reactions of the female sex.

The habitus resembles that of male eunuchoidism for the same physio-pathological reason, and presents the same long-limbed tallness, thinness, undeveloped musculature, white delicate skin, abundant head hair and poor body hair. It is the asthenic visceroptotic habitus. Special features are the under-development of the breasts and the narrowness of the pelvis, which is infantile, not android. Here also the head is triangular, the lower jaw recedes, and the teeth are decalcified and prone to sepsis, needing many stoppings which fall soon after insertion. The central incisors are large, the lateral incisors small, the canines blunt (the hypogonadal dental stigma). Hands and feet are long, fingers and toes very long.. The whole appearance is infantile.

The hyposexuality is characterised by late onset of menses, irregularity and prolongation of the interval, scantiness of flow. The irregularity and lengthy intervals may occur at onset or after a period of regular menstruation. Dysmenorrhœa exists but is not a characteristic symptom. It is due not to the hormonal disturbance but is a reflection of the hypersensitivity of the patient. Fertility is impaired. Libido is decreased, in some cases to the point of frigidity or even to aversion to sexual activities. Libido is sometimes ambivalent, an infantile trait. Local exploration of the genitals reveals a small and infantile uterus. The endometrium is atrophic, but less than in climacteric disease. The vaginal smear shows diminution of cornified cells and glycogen, and a lowered acidity of the secretions. The work of Papanicolaou has shown the importance of following up the vaginal smear for diagnosis and judgment of therapeutic results.

The eunuchoid psychology is due mainly to the failure of œstrin to exert its normal sex-maturing influence on the cerebral cortex and in some cases to coincidence of hypothyroidism. It is also due, possibly to an even higher degree, to psychogenic factors of reaction to the sense of inferiority engendered by the disease. These patients feel themselves to be abnormal women because of the difficulties in menstruation, to which so much importance is attached psychologically that we can adapt Virchow's dictum and say: "Woman is the appendage of her menstruation." The frigidity and sterility make them feel even more inferior, and when they see their breasts larger, their periods regular and sexual intercourse pleasurable after treatment, their first words are: "I feel a normal woman again."

Young hypo-œstrinics are submissive and of sweet disposition, but although mild, gentle and tearful they are very touchy, always feeling slighted or fearing that they will be slighted. They are sensitive to every social influence, full of notions and whims, very imaginative and excitable. They are distinctly introverted, the introversion appearing in the mild forms as shyness, in more accentuated cases as day-dreaming, enclosure within the self, a liking for solitude, a downright shunning of company. Sadness is added to these symptoms. It occurs in waves, and ranges from simple moroseness to melancholy. In these young hypo-œstrinics it is a clinging lachrymose sadness, differing from the proud melancholia which older hypo-œstrinics keep to themselves.

Emotivity with its corollary anxiety is another dominant feature. Such

patients vibrate intensely to all joys and sorrows, especially to sorrows. They burst into tears at the slightest provocation, and weep when relating their symptoms or without any reason in the consulting-room. Their anxiety is directed to themselves and to their parents, to whom they cling. It is often vague, however, " a feeling in the head " or stomach, a general tremulous fear as if death were imminent. Irritability is not common, contrary to the finding in older hypo-œstrinics.

Psychosis occurs in predisposed individuals and when certain other factors, organic and psychogenic, are added. It takes the form of schizophrenia or melancholia. The hypo-œstrinism is a contributing factor, setting the psychological pattern of the psychotic reaction. Hypo-œstrinic depression is the basis of the psychotic melancholia, and hypo-œstrinic introversion the basis of the psychotic schizophrenic reaction.

Background symptoms. These are more accentuated than in male eunuchoidism. The reactivity manifestations are important. A prominent symptom is asthenia, a chronic fatigue felt especially in the back. These patients feel tired as soon as they waken, drag through the day with difficulty and go to bed exhausted, but external stimuli improve their condition and the asthenia yields to absorption in other interests.

Another important reactivity manifestation is represented by attacks, often prolonged, of febricula or fever, a neuro-vegetative fever such as I described in 1920 for hyperthyroidean conditions and which has caused many such patients to be sent to sanatoria for tuberculosis. Here also it is due, in my opinion, to a hyperthyroidean state. The hyperthermic reactions are usually pre-menstrual or menstrual. Such patients are predisposed to peptic ulcer but not, as is usually thought, to tuberculosis, the latter opinion being due to the frequent misdiagnosis of eunuchoids as tuberculous.

The most important organic manifestations are digestive. Next come tachycardia with palpitations, rheumatic manifestations and acne.

Digestive disturbances, which are frequently the direct cause of the consultation, consist in pain, dyspepsia, constipation and that so-called mucomembranous colitis which is not a colitis but a manifestation of overstimulation of the colon parasympathetic. These disturbances are often bound up with visceroptosis which, described as a separate disease (Glenard's disease), is a manifestation of hypogonadism, œstrin as well as testosterone seeming to exert a strong influence on the tonus of the digestive tract. As I showed a long time ago, digestive disturbances in such visceroptotics are not due to the mechanical troubles caused by this infirmity but are frequently independent of changes in visceral position. Gastroenteroptosis may contribute and should be treated, but not as in elderly eunuchoids with belts and bandages, which have a deleterious psychological influence as well as a physical influence which may lead to hypotrophy from disuse of the abdominal muscles, but with constitutional therapeutic methods, including endocrinotherapy.

Another group of digestive disturbances, met more often in female than male eunuchoids, comprises the acute abdominal attacks which are the source

Fig. 8
FEMALE CEREBROPITUITARY EUNUCHOIDISM

of important mistakes in diagnosis.

They usually occur near the period and simulate appendicitis or gall-bladder disease, accompanied by vomiting and a rise in temperature. Such cases are usually misdiagnosed and unnecessary operations are performed. As the intervention brings no relief another is advised. First the appendix is removed, and then as pain persists the gall-bladder is taken away. The continuance of symptoms moves some surgeons to " fix the colon " or " remove adhesions," and as a last phase of the tragedy to remove a " cystic " or " sclerotic " ovary, a procedure which of course aggravates the condition. These patients end by being real physical and mental wrecks. I have described their state by the term " vandalistic syndrome," which will continue appearing in practice until a more definite constitutional and endocrinological way of thought penetrates into diagnosis and treatment of abdominal conditions.

Tachycardia and palpitations are frequently encountered. They arise from disturbance of the autonomic innervation of the heart caused by defective ovarian secretion or through a secondary thyroid reaction. Anæmia of hypochromic type is a common finding—the old " chlorosis " was ascribed by some clinicians to ovarian insufficiency. In point of fact it seems due not to the basic disturbance of the œstrin system but to coincidental disturbances of other neuro-endocrine systems such as the hypothetical pituitary hæmopoietin, thyroid or cortin systems.

Fibrositis and arthritis are seen but less often than in older eunuchoids. Fibrositis is more frequent, osteoarthritis being the affliction of older patients. These rheumatic manifestations are the result of the abnormal metabolites produced through hypo-ovarism on constitutionally defective joints (Cawadias). Other cases of osteoarthritis, which the Americans aptly call hypertrophic arthritis, are probably determined by a reactive hypersecretion of antepituitary growth hormone.

Acne is very frequent. Modern research has connected acne with the testosterone action, and it is probable that in these eunuchoids the testosterone normally present in women acts unchecked by the inadequate amount of œstrin and causes this symptom.

Biochemical Syndrome. The following are the most important findings:

1. Diminution of basal metabolism. This is encountered only in some cases, and is probably due to coincident hypothyroidism. At all events, when the basal metabolism and the temperature are determined throughout the whole menstrual cycle in women, they show peaks at about the 12th and 27th days, *i.e.*, coinciding with the peaks of œstrogen secretion. These peaks are not observed in female eunuchoidism.

2. Increase of creatine in urine. This is connected with failure of the gonadal regulatory function regarding creatine metabolism.

3. Diminution of œstrogens in the urine. Androgens are normal.

4. Negative reaction for pituitary gonadotropins in the urine, signifying that gonadotropin is either normal or diminished.

Paracme. Female eunuchoidism is an essentially chronic condition,

although greatly relieved and even cured by modern methods.

At a late phase obesity of pituitary type develops. Digestive manifestations increase and duodenal ulcer often develops. Mental manifestations also increase in severity. The whole condition is aggravated by the multiple unnecessary operations to which such patients are subjected (the vandalistic syndrome).

Life is shortened if the condition is left untreated. These patients are fragile vessels, more delicate than their male counterparts because of the greater intensity of the digestive and mental manifestations.

The Post-puberal Hypo-oestrinic Eunuchoid. When hypo-œstrinism occurs after full development of the genital organs, and particularly after the thirtieth year, the clinical picture differs. Macroskelic tallness does not occur, except when the late eunuchoidism is the projection into middle age of an early eunuchoidism. Thinness, however, is much more accentuated, and combined with general relaxation and a sallow, gerodermic skin gives an impression of senility accentuated by the prematurely grey hair. The facies is characteristic. The expression is dull, tired, empty, and the sallow, often puffed skin is commonly covered with brown freckles and wrinkles—not the sharp lines of the thinker but those due to flabbiness from disturbed trophicity. In some cases the aspect is virile through reaction of the adrenal cortex. The rest of the body shows the same cachectic features. The breasts are atrophied. The abdomen is very lax, its walls falling in folds. Axillary, pubic and in some cases scalp hair coarsens and falls. All this is determined in great part by a coincident hypothyroidism.

Psychologically these patients differ from young eunuchoids. Intellect is often dull, as shown by the face, as a result of the hypothyroidism, whereas young eunuchoids are cerebrally very lively. Instead of the dependent, clinging and sweet disposition of the young, sadness and depression dominate. This sadness has a trace of pride, and these subjects keep their griefs to themselves, shutting themselves into their own life and preferring solitude. Joy is completely absent and they cannot appreciate the delightful things of life. After this proud melancholia irritability is a characteristic feature, absent in young eunuchoids. In company they are irritable and even spiteful, venting their spite on those they love best. They cannot tolerate contradiction or any opposition to their opinions. A third psychological feature, met in advanced cases, is a characteristic change in their affections, seen in nearly the same form in climacteric disease. They feel no affection even for their families, and I have often heard such patients say: "I know I ought to love my husband and children. I did once but now I have no feelings for them." Not only are the affections stilled but they are often replaced by aversion. A particular aversion to the male sex, particularly from the sexual point of view, is noted, and probably represents a psychogenic defensive mechanism. And dominating all is a deep indolence and aversion to occupation.

The other element of the eunuchoid triad, the hyposexuality, also offers some special features. Menstrual disturbances, diminution of flow, irregu-

larity, abnormal length of the interval and even complete amenorrhœa, are more marked than in the young. Leucorrhœa also occurs. It is bound up with the general condition and thus is not to be treated with tampons. Metrorrhagia may occur through reaction of other endocrine systems. Malposition of the uterus and even prolapse are common, and related to the general laxity of the body from œstrin insufficiency. Such patients feel their pelvic laxity. They have a bearing down sensation as if their viscera would fall downwards. They feel that they need a bandage to support these parts, and get relief from sitting down and crossing the legs. Support by means of abdominal belts, provided they are correctly fitted, is helpful, but before such a belt is prescribed the patient should be tested by holding the abdomen with the hands forming a girdle.

Among the background symptoms asthenia, digestive disturbances and rheumatic manifestations offer special features. Asthenia is much more severe than in young eunuchoids and tallies with their cachectic appearance. These patients feel tired from morning to night and in accentuated cases are incapable of any effort. They feel their fatigue in the back, which in many cases is painful, the pain aggravating their asthenia. They faint easily. The general impression is of a tired back-aching female. Often, however, despite the asthenia these women need movement. The sluggish state of their body requires exercise, sometimes violent, to keep it in comfort.

Anorexia is frequent, also a craving for certain foods. Digestive disturbances are much more accentuated than in the young, and in fact these patients usually seek help for these and not for their basic state. They are usually conscious of an upset stomach. They get up in the morning with an "all-gone" feeling in the abdomen. Distress and fullness of the stomach are followed by belching and uprising of mucus. Nausea is felt strongly on rising. Eating does not relieve these symptoms. During the day similar disturbances occur irregularly, with gnawing hunger, attacks of flatulence with abdominal rumblings, and nausea. Some of these patients experience attacks of flatulence in the night, and their sleep is disturbed as a consequence. Constipation is very marked. Pills and laxatives are abused. With older patients the bowels are a real obsession, for flatulence as well as the constipation. In spite of laxatives stools are difficult and slow, and even after going to stool there is always a sensation of a lump remaining in the rectum. The abdominal walls are very flaccid, palpation of the digestive tube is easy. Visceroptosis is accentuated. All these disturbances are due to defects of the innervation of the digestive organs due to the glandular disturbance. There is a great element of liver insufficiency.

Rheumatic manifestations are nearly constant. In their milder form they appear as "fibrositis," with pains all over the body, chiefly in the neck, and a cracking sound when the patient turns. A lumbar localisation of fibrositis also is very common. In more severe cases osteoarthritis (the hypertrophic arthritis of the Americans) occurs, probably determined by a reactive hypersecretion of pituitary growth hormone. The most frequent forms are

Heberden's nodes, Bouchard's nodes (osteoarthritis of the second interphalangeal joint and of the knees.

In many cases a reaction of the posterior pituitary causes obesity. The eunuchoid is fat instead of thin, with an obesity of a form to be described with pituitary obesity. The other features are similar to those already described.

Therapeutics. *Psychotherapy, dietotherapy, physical medicine, general constitutional pharmacotherapy.* These are the basic procedures in treatment of cerebro-pituitary eunuchoidism, endocrinotherapy being reserved for special cases.

Psychotherapy ranks first for such patients. Their mental conflicts are often very violent, and the endocrinologist should try to understand them and bring calm into their broken lives while using organic methods. If some clinicians succeed with hormones which prove ineffective in the hands of laboratory workers it is because good clinicians combine hormones with brains and enhance their treatment with psychotherapy. Sterility in particular is the despair of many eunuchoids and much tact is needed to deal with this conflict.

Diet should be rich in proteins and well-balanced in vitamins.

Of physical methods ultra-violet irradiation is so effective that, as I pointed out in a previous work, it can be regarded as a physical endocrinotherapy. Ultra-violet irradiation, according to certain authors, stimulates the cells of the skin to secrete œstrogenic hormones. At the St. John Clinic I have seen eunuchoid patients improve on this method alone. High altitude climates such as the Engadine have given me excellent results, and I believe that similar effects could be obtained from climatotherapy in the Eastern Scottish Highlands.

Among general constitutional pharmacotherapeutic agents sedatives and tonics are used according to indications. Iron is particularly indicated in anæmia. I have obtained good results from certain homœopathic preparations of pulsatilla and sepia, administered according to the rules of the homœopathic materia medica. Intensive parenteral B complex treatment, ascorbic acid and thyroid, however, are the best general constitutional methods.

Endocrinotherapy. This is a valuable addition to treatment of cerebro-pituitary eunuchoidism, provided it is used in combination with the preceding methods and other constitutional pharmacological agents. Except for certain mild procedures of oral endocrinotherapy, it is indicated only for states of abnormal thinness, tallness and cachexia, serious menstrual and psychological difficulty. Its application demands care and skill. It has been abused, and to-day the disasters wrought by the injections of ostrogens given to young girls " to bring on the period " are becoming apparent. Besides the organic insult of such haphazard treatments there is the psychical trauma bound up with parenteral treatments given to such sensitive and suggestible individuals as young eunuchoids.

Endocrinotherapy should start with the oral thyropituitary method, which is both beneficial and easy to apply in general practice. Capsules or cachets containing thyroid 0·02–0·04, anterior pituitary 0·05–0·15 and total ovarian

extract 0·15–0·30 are given. Dosage can be modified according to indications, but a rough indication is two capsules per diem for five or six days of the week.

In more severe cases, however, the gonadotropin procedure is indicated. *B*-gonadotropin inhibits the follicles. Therefore chorionic gonadotropin preparations (Antuitrin S, Gonan, Pregnyl) should not be used, except in some cases as a complement of *a*-gonadotropin preparations. *A*-gonadotropin in certain antepituitary preparations, principally in pregnant mare serum preparations (Serogan, Gestyl, etc.) is indicated. About 5,000 units should be given in the first two weeks of the cycle and treatment repeated for many cycles. As antihormones may develop it is often prudent to allow a cycle to pass without treatment. The sensitivity of the patient to the particular preparation should be tested before intensive treatment is started. Copenhagen workers (Rydberg and Pedersen-Bjergaard) advise for severe cases a combined gonadotropin procedure. Five daily injections of 3,000 I.U. of equine serum gonadotropin are followed by three injections of 1,500 I.U. of chorionic gonadotropin given on alternate days. According to the Copenhagen workers menstruation occurs 10 days after the last injection.

Œstrogens and progestin come next into consideration. In some mild cases small doses of natural œstrogens or stilboestrol are given during the first half of the cycle for a few cycles. Treatment should not be prolonged because œstrogens depress antepituitary gonadotropic secretion, although this effect is not pronounced with small doses. In more severe cases œstrogens can be given parenterally during the first half of the cycle and followed by progestin during the days preceding menstruation. This method is indicated in conditions with uterine hypoplasia as a preliminary to the gonadotropin procedure. It is indicated by itself in conditions of abnormal tallness, thinness, and nervous manifestations. By itself this procedure does not restore the cycle to normal but brings about menstruation, which in some cases is valuable.

The combined œstrin-progestin method, as perfected by Zondek, consists in injecting on two consecutive days 12·5 mg. of progesterone combined with 2·5 mg. of estradiol benzoate. Bleeding occurs about five days after the last injection.

There is first a psychological effect. After menstruation, particularly in women who have never menstruated, the personality is completely changed, with more optimism, more confidence, more femininity. The dress and general appearance change, these patients become more mature, their breasts develop and sexual desire and emotions are felt. Particularly in eunuchoids with "primary amenorrhœa," the zest for life is renewed. I cannot help believing that there is also an organic effect. Our fathers were probably right in considering that menstruation effects a certain metabolic detoxication. Emmenagogues were, for physicians of old, valuable "alterant" medicines, used to improve the constitution. There is much truth in the observations of these old physicians.

The technique of the endocrinotherapy of female cerebro-pituitary eunuchoidism is delicate and can therefore be given only in general outline.

In unskilled hands much havoc can be wrought (except from the oral thyro-pituitary method); but deep knowledge of the action of these preparations, strict following up according to the clinical empirical method and combination with other general constitutional measures can restore many unfortunate eunuchoids to a normal life of femininity and motherhood. I must, however, state frankly my opinion, that endocrinotherapy of eunuchoidism is not a method of general practice.

Primary Ovarian Hypo-œstrinic Eunuchoidism.

In primary ovarian hypo-œstrinic eunuchoidism the responsible hypo-œstrinism arises from a disturbance of the glandular ovarian centre of the œstrin system, *i.e.*, from factors acting directly on the ovary. Infections act through the mechanism of ovaritis. The most important are mumps, gonococcus and probably tuberculosis, which acts not through its specific inflammatory reactions but by wider cellular ovarian disturbances caused by the soluble toxins of Koch's bacillus. Toxic factors also act by setting up a toxic ovaritis, the most important being alcohol, morphia and lead. Malnutrition can affect the ovaries directly by disturbing their normal development and function. This mechanism, whether general or in the form of particular avitaminoses, enters into consideration of the numerous eunuchoidisms from malnutrition seen in the starving Europe of to-day. A genogenic inferiority of the ovary is an important factor of predisposition.

The physiopathology is similar to that of cerebro-pituitary eunuchoidism except that the hypo-œstrinism begins in the ovary and the pituitary may show compensatory hypersthenic reactions. These, however, are less distinct than in castration eunuchoidism.

The clinical history also resembles that of cerebro-pituitary eunuchoidism, except for the special etiological constellation and the lower degree of the symptoms. Therapeutics is also similar, except for the procedures indicated by the special etiology. *A*-gonadotropin, however, seems less effective and it is often necessary to use œstrogens, which confer symptomatic relief.

Congenital Hypo-œstrinic Eunuchoidism

This disease, which includes what is described as utero-ovarian hypoplasia, is determined by a genetic and thus congenital deficiency of the endocrine ovary reaching the stage of hypoplasia and even aplasia. Distinct cases of complete lack of ovaries have been described, as also cases in which ovarian tissue is found only microscopically. Wilkins has collected twelve cases in which the ovaries never developed beyond the stage of the genital ridge which is found in embryos of 5-7 millimetres. In most cases, however, there occurs simple hypoplasia or the ovaries may show a normal macroscopic appearance but great development of connective tissue and poverty in follicles on microscopic examination.

The clinical syndrome is one of severe eunuchoidism, but with certain special features.

1. The habitus is not always typically eunuchoid. Instead of macro-

skelia, microskelia is found (the inadequately termed pituitary proportions). Dwarfism is frequent, and the ovarian dwarfism described by Albright and his co-workers belongs to this form. In my opinion the dwarfism is not due to the ovarian insufficiency but to a coincidental genetic defect.

2. Hyposexuality reaches a high degree, and such cases include most "primary amenorrhœas."

3. There is an excess of alpha-gonadotropin in the urine as in castration and menopausis.

4. Other genetic defects often co-exist. Turner's syndrome consists in the association of congenital hypo-œstrinic eunuchoidism (utero-ovarian hypoplasia) with a congenital webbed neck and cubitus valgus. Congenital ocular abnormalities such as bilateral ptosis, bilateral cataracts and squint are often encountered.

Much can be done by endocrinotherapy for such patients. In mild cases early œstrin-gonadotropin treatment may counteract the bad direction given by the genes in sexual development. In most cases œstrin-progestin treatment brings menstrual periods and improves tremendously the psychological condition of the patient.

CHAPTER XXIV

FEMALE EUNUCHISM

Female eunuchism is a disease characterised by total ovarian deficiency due to removal or destruction of the ovaries. It is the female castration disease. Under this heading come cases of bilateral destruction, or very extensive destruction, of the ovaries. Unilateral or limited destruction of the ovaries results in a clinical syndrome approaching that of eunuchoidism.

The first case of female eunuchism was described by Percival Scott in 1750, according to Kuzrock. Scott had operated on a patient with bilateral hernia by resecting the hernial sacs without opening them. The ovaries were in the sacs. Since McDougall's introduction in 1850 of ovariectomy, more opportunities have occurred for detailed study.

In female eunuchism there occurs primarily a complete and sudden ovarian deficiency. Thus the physiopathology of the condition is up to a certain point similar to that of eunuchoidism, the difference being essentially one of degree. The essential physiopathological difference is that in eunuchism the reaction of the non-ovarian endocrine systems differs from that occurring in eunuchoidism, the disturbance being more sudden and more complete. These reactions have been studied principally experimentally. In the anterior pituitary eosinophiles and basophiles increase, and special castration cells develop. The antepituitary hyperfunction results in excessive *a*-gonadotropin secretion, which is found in the urine in excess. The thyroid also enters into a state of hyperfunction.

Symptomatology. The morphological syndrome is similar to that of eunuchoidism, as it depends essentially on œstrin deficiency. Pre-puberal

castrates develop the typical eunuchoidal habitus. Girdle obesity develops later, as in eunuchoidism.

The sexual syndrome is one of intense maldevelopment of the genital organs in pre-puberal castrates, and of retrocession and atrophy of these organs in post-puberal castrates. The vaginal smear indicates advanced atrophy of the vaginal epithelium. Menstruation and fertility are of course totally absent. Libido may be diminished or absent as in eunuchoidism, this occurring mainly in pre-puberal castrates. However, libido may persist even in such castrates but principally in older castrates, as a result of the reactive hypersecretion of *a*-gonadotropin which directly influences the nervous regulators of sexual function, and chiefly because of factors of psychological compensation affecting the same nervous regulators. Libido may even be exaggerated through freedom from the fear of pregnancy.

A special circulatory vasomotor syndrome consisting in flushes of heat, not encountered in eunuchoidism, is very characteristic of eunuchism and may take its appearance in the days following castration. It feels as if inside the body a glow of heat is rising to the face, which becomes red, hot and flushed. Finally the heat ends in sweat. Sometimes the patient has the sensation of hot steam rising within the body and breaking up in sweat. These patients fan vigorously, unable to fan fast enough. All windows and doors are thrown open. These flushes come either spontaneously or else after a stimulus such as emotion, excitement, exercise or sometimes eating. They are worse in summer and are aggravated when the patient is resting covered with bedclothes. This is a vasomotor phenomenon of vasodilatation. It is not always of purely endocrine origin (thyroid reaction?). Psychogenic factors are important. Reynolds noted that certain of his ovariectomised patients were not relieved of this symptom by œstrogens or phenobarbital, but reacted well to correction of their neurosis made possible by intensive and careful study of their personality.

The mental syndrome differs in many points from that of eunuchoidism, particularly in post-puberal castrates. Protest against the sexual trauma dominates the psychopathology of these patients. Introversion is noted, but it is an introversion of anger against the mutilation. Irritability is very marked. Indifference, arrogance and various anti-social reactions develop.

Biochemically fall of basal metabolism and creatinuria are seen, as in eunuchoids. One hormonal finding, however, is very characteristic, an excess of *a*-gonadotropin in the urine.

The disease develops chronically, although it may be subdued up to a certain point by modern methods of treatment. Female eunuchs are less frail than eunuchoids and thus more resistant to infections and less liable to have their life shortened by their disease. Mental disturbances, however, are more frequent and more severe.

Therapeutics. General constitutional methods, particularly psychotherapy, play a preponderant role. The patient must be helped to rid herself of the conflict caused by her mutilation. Œstrogens, however, are the basic thera-

peutic agents, and have completely changed the outlook on this disease. Œstrogens act by depressing the antepituitary, whose hyperfunction is the cause of the most distressing symptoms of eunuchism. Dosage and technique of administration should be individual. Œstrogens should be administered orally, and only in exceptional cases should recourse be made to injections. The procedure is a substitutive treatment and must be continued throughout life, like insulin treatment in diabetes, but the introduction of orally active synthetic œstrogens makes the treatment more comfortable and convenient than other substitution treatments. The subcutaneous implantation of œstrogenic hormone tablets promises a high degree of perfection in the treatment. Ovarian grafts are unnecessary.

Progestin can be used as an adjuvant to œstrin treatment, as it exerts a similar depressant action on the anterior pituitary. Kaufmann provoked menstrual cycles by a combination of œstrin and progestin, repeating the normal hormonal cycle. This is an unnecessary experiment. Total ovarian extracts by mouth are often helpful in alternation with œstrin injections. Thyroid is effective as an adjuvant in some cases. Insulin with glucose can be given in certain cases with emaciation.

CHAPTER XXV

FEMALE CLIMACTERIC DISEASE

The climacteric is a normal phase, a critical phase of life bound up with the mysterious biological rhythm, and is initiated and characterised by involution of the gonads, which thereafter play a secondary role in biological processes. It is the converse of puberty, another critical phase of life but based on the start of activity in the gonads, which from that time until the climacteric play an important role in life. Climacteric is common to both males and females. In females the climacteric gonadal involution is manifested by cessation of menstruation, menopausis, which is often taken as synonymous with female climacteric. This, however, is inaccurate, for climacteric is something more than menopausis and in fact starts before menopausis. In men there is no striking sexual manifestation such as menopausis but merely a slow diminution of potency and libido. The date of appearance of climacteric varies in men and women. In women it is earlier and corresponds roughly to the early fifties, whereas in men it occurs in the late fifties. With progress in civilisation and hygiene the onset of this phase of life is shifted to later dates.

Climacteric being a normal phase of life, it should develop without symptoms. When symptoms occur there is climacteric disease. Thus climacteric and climacteric disease are not synonymous, the former being a biological phase of life, the latter expressing a pathological disturbance of that phase. The outstanding recent study of this disease has been given by Maranon.

Physiopathology. Involution of the ovaries, and thus hypo-œstrinism, in late life is a normal phenomenon. Normally this break at the œstrin element

of the system of constitutional regulation is compensated by the other elements of this system, mainly endocrines and psyche. An adequate compensation makes the climacteric phase silent. An imperfect compensation makes for climacteric disease.

The constitutional regulator initially disturbed is the gonad. The œstrin system enters into imbalance. There occurs hypo-œstrinism due to ovarian involution, thus a primary hypo-œstrinism. At first the diencephalo-*a*-gonadotropin system reacts hypersthenically in compensation, but later this component of the œstrin system enters into hypofunction and total hypo-œstrinism is established.

Nearly all other neuro-hormonal systems become disturbed in their effort to compensate the imbalance of the constitutional regulatory systems initiated by the involuntary hypo-ovarism. Pituitary fat-metabolic hormone disturbance causes a special obesity. An abnormal reaction of the adrenocortical system causes a special form of obesity, virilism, hyperpiesia, atherosclerosis. An abnormal thyroid reaction is evidenced by symptoms of hyper- and hypothyroidism. The adrenalin system and the sympathetic component of the system of constitutional regulation react by hyperfunction, determining in particular cardiocirculatory disturbances.

It is the psyche, however, that is predominantly disturbed in its efforts to compensate the total imbalance, and the psychological disturbance is a preponderant physiopathological as well as clinical manifestation of female

Etiology. Female climacteric disease occurs at the phase of climacterium, usually between the ages of forty-five and fifty. It begins either before or more rarely after menopausis. It is of very great frequency. Three groups of etiological factors enter into consideration.

First come factors determining premature and intense involutional hypo-ovarism. In such cases the other neuroendocrine systems and the psyche have not sufficient time to adjust the compensatory balance. The responsible factors are diathetic (mainly a genetic inferiority of the ovarian system), infections localising on the ovary or upsetting the ovarian system as a whole, and sexual fatigue.

Next come factors determining abnormal compensatory reaction from other neuroendocrine systems. These consist in a general neuroendocrine imbalance due to genetic and environmental factors.

The factors of greatest importance, however, are those determining an abnormal psychological reaction. Normally women accept with some degree of serenity the cessation of their sexual life, particularly women of the middle classes who have devoted themselves to domestic affairs and rearing their family. These pass placidly through the climacterium surrounded by their grown-up children and satisfied by the accomplishment of their task. In such cases there is normal and complete psychological adaptation, a normal mental attitude to the climacteric episode. But many women show abnormal psychological reactions to the involutional hypo-ovarism. These abnormal reactions

are bound up with the personality of such patients. Two groups can be distinguished. The first group is composed of women, usually of the higher social strata, living an intense social life. They attribute exaggerated significance to love, beauty and social success and try to get out of life all they can. Poor in spiritual background, they strive after non-essential emotions, often with restlessness and anxiety. When at the climacterium these women note their fading looks, the start of a middle-aged spread and the greater success of younger women in pleasing men, they are disturbed in their mental life. The stoppage of menstruation, that apparent symbol of femininity and sexuality, is for them the knell of the most highly prized part of life. Their system of constitutional regulation is broken at its mental link. The other group, on the contrary, comprises those women who have lived narrow lives. Deprived by nature of good looks and vitality and by fortune of a happy married love life and social activities, sexually frigid, introverted, bad mixers and full of mental intolerance, they have been unable to enjoy life's pleasures. They have taken little and given little. They may have had romantic dreams but have been incapable of asserting their femininity and sexuality, often entrenched as in a fortress by their rigid code of duty or prejudice. In these women the cessation of menstrual bleeding, again the symbol of femininity, motherhood, sexuality, engenders panic. They feel the emptiness of their lives, they feel they are passing into old age without experience of the joys of love.

This psychogenic factor of climacteric disease is of the greatest importance. Its study gives more insight into the condition than determination of the rat or mouse units of œstrin or gonadotropin in the urine. I have recently had referred to me an unhappy woman who had developed after menopausis severe attacks of flushes of heat. Œstrogens in enormous doses had been of no avail, and I was asked whether any other hormonal treatment could be tried. What those who had treated the woman had failed to recognise was the great narrowness of her life, an enforced spinsterhood due to an unhappy love affair and to a milieu of Calvinistic rigidity. She was rich and of good standing, she could have had of life whatever she wanted . . . These matters are not connected with œstrogens.

Symptomatology. *Onset.* Female climacteric disease begins slowly and insidiously some two or three years before menopausis and more rarely a year or two afterwards. The woman feels she is becoming less strong. She cannot dance and play games as she has always done. She feels irritable and complains of flushes of heat. The face looks tired and the waist widens in the middle-aged spread. When onset of climacteric disease is pre-menopausal menstrual irregularities may occur. The periods come at longer intervals and many are missed. In other cases violent hæmorrhage occurs. The disturbance of menstruation, however, is not commensurate with the severity of the disease, and in many serious cases of climacteric disease of pre-menopausal onset periods are normal.

General symptoms. Obesity, flushes of heat, asthenia, intense psychological and sexual disturbances occur.

Obesity is usually of the so-called pituitary type, and is in fact due to abnormal pituitary fat-metabolic hormone secretion. It starts as a simple trochanteric obesity and develops slowly and steadily into the " middle-aged spread " and typical girdle, mons and mammary adiposis. The face also is involved and becomes round with a double chin, but the extremities escape. This adiposity may attain enormous proportions. In some cases, when a hypothyroidean element is added, adiposis is more generalised and extends to hands and feet, which are coarse and infiltrated, and more intensely to the face, which also is infiltrated. In rarer cases the obesity assumes a cortico-adrenal type through a reactive hypercorticogenitalism. Here fat accumulates on the upper part of the body, above the umbilicus, and the face, constantly full-moon in such cases, takes on the typical plethoric appearance.

Flushes of heat and asthenia are prominent reactivity reactions. The flushes of heat, probably due to a hyperthyroidean or vagal reaction, resemble those described in female eunuchism, the patient feeling as though boiling water were entering the chest and head. Asthenia, physical and mental, is an important and often initial symptom. Patients feel tired, especially in the morning, brighten up during the day when absorbed by their occupations, but again feel limp in the evening. They restrict their activities and no longer have the wish to go on.

Sexual disturbances occur, bearing on both physical and mental aspects. Physically they vary. Sometimes the periods stop abruptly, in most cases they become shorter and more irregular until they stop, and in other cases the stoppage is preceded by menorrhagia or even metrorrhagia. After apparently ceasing the period may return after months or even years. S. Levy described the case of a woman who had had fourteen pregnancies and whose menses stopped at the age of 60 but returned between the ages of 75 and 78, coming in a regular 28-day cycle and lasting for six days. It should be remembered that menstrual disturbances occurring at the climacteric may be due not to the climacteric but to various gynæcological diseases developing at that stage, and gynæcological examination is of the first importance.

Libido is disturbed. In many cases sexual feeling is suddenly quenched, and may be converted into deep aversion for the opposite sex. This is quite different from the gradual waning of the sexual impulse which occurs in normal climacterium, and indicates a psychogenic factor. The dramatic change of libido renders sexual relations intolerable, and often causes the woman to seek medical aid. In another class of case the contrary occurs, libido increasing from psychogenic action as well as from pituitary gonadotropic hypersecretion, and these women may launch into amorous adventures for the first time in their life and commit such follies as maintaining a gigolo. In exceptional cases libido may assume an active homosexual trend through a reactive hypercortico-genitalism.

The clinical picture is dominated by the psychological disturbances. They may occur long before any physical manifestation. The cerebral cortex seems to be an extremely delicate reagent to the changes of body chemistry ensuing

from the involutional hypo-ovarism, and in addition, as has been said, psychogenic factors loom large in this important critical phase of woman's life.

Irritability and impatience are the initial and dominant traits. Women from easy-going become impossible to live with. Previously good wives and mothers, they feel that husband and children " get on their nerves." Everything worries them, household duties and relatives. Their conversation becomes sharp and bitter. Their irritability interferes with their work. As a patient of mine, a writer, expressed herself: " I am so irritable that it is hard for me to fix my mind on any work. I cannot bend my mind to the subject but think of something else, worry about something else . . . After writing a letter and re-reading it I find everything wrong. I have used wrong words and expressions and finally give up the letter in disgust." When an adrenal virilising reaction occurs the violent domineering tendency is accentuated (menopausal virago). Jealousy is often fiery, particularly about the success of others. Loquacity often completes the manifestations of the irritability.

Anxiety dominates in many cases. It is usually of vague diffuse type, with fear of life, dark forebodings about the future, but may centre on the personal health, on heart and stomach (the old anxiety neurosis). Fear of insanity is quite common. I have often noted in climacteric women and men a feeling described by French psychiatrists as twilight anxiety, an inexplicable feeling of depression and sadness which increases with the darkening of the day and disappears in brilliant artificial light.

Indifference and sadness complete the picture of the emotional make-up. The indifference may be great. The woman does not care what happens and is apathetic to husband and children. She has no ambition. She wants neither to work nor to amuse herself. In other cases sadness predominates. It overwhelms the patient in waves. It is usually a proud melancholia in which the woman wraps herself, disdaining to air her sufferings and dark outlook. Dullness of the mental faculty is frequent. Complaint of failing memory is frequent, and manifests a hypothyroidean element. Words come slowly and have to be dragged out to express ideas. Insomnia is common and is probably due to a hyperthyroidean element. Drowsiness due to diencephalo- post-pituitary reaction is less often seen.

More severe mental disturbance is manifested by syndromes of dementia and silliness due to atherosclerotic lesions of the cerebral cortex, and by involutional melacholia. This is an indirect manifestation of the complex endocrinopathy which is the basis of climacteric disease. In other words, it occurs in pre-disposed subjects and the endocrinopathy does not cause it but serves to make it manifest. However, œstrogenic hormones have produced some triumphs, and even women near to certification have pulled out of their terrible state by the skilled use of this method.

Organ syndromes and laboratory explorations. Nervous, cardiocirculatory and rheumatic manifestations become apparent. The nervous manifestations are usually due to vasomotor disturbances, and consist in cephalalgia,

vertigo, various neuralgias, numbness and tingling in the forearms, fingers, legs and toes. The eyesight fails, and ear noises are a constant source of worry.

Cardiocirculatory disturbances are less important here than in male climacteric disease. Palpitations and tachycardia from a hyperthyroidean reaction or nervosism are noted. Hyperpiesia is a very frequent finding, and is often characterised by very high sphygmomanometric readings, much higher than those found in man but of less serious prognostic significance. Atherosclerotic manifestations occur. Hyperpiesia and atherosclerosis represent the adrenocortical reaction.

Pollakiuria often occurs without renal disturbance but from neurovegetative disturbances. Kraurosis vulvæ, pruritus vulvæ and other dermatoses develop and are greatly relieved by œstrogens.

Climacteric arthritis is a common manifestation of female climacteric disease. It is probably due to eosinophil pituitary reaction and is often of hypertrophic type, anatomically similar to that found in acromegaly (osteoarthritis). The fibrositic type, however, is often observed. This "chronic rheumatism" may be an oligosymptomatic form of female climacteric disease and is greatly relieved by œstrin.

Constipation is a fairly constant feature. Many women previously healthy in this respect develop constipation at the climacterium. Anxiety as to the existence of a more serious disease may be expressed, and investigation should be complete to eliminate neoplasm, for instance. Climacteric constipation is troublesome, tenacious, aggravates the whole condition and needs careful attention. It may give rise to secondary B. coli infections of the urinary tract.

The biochemical syndrome in female climacteric disease depends on the various endocrine involvements and therefore does not lend itself to a standard description. According to the mode of involvement of the thyroid and other glands abnormal findings in respect of basal metabolism, blood sugar, blood and urinary nitrogen, may be elicited.

The hormonal syndrome is more characteristic but varies according to the phase of the disease. At onset the principal finding is an increase of œstrogen in blood and urine. In a second and longer phase blood and urine show diminished œstrogen but high values of *a*-gonadotropin appear in the urine. Later even *a*-gonadotropin decreases in the urine and finally disappears.

Course and termination of the disease. Nowadays, thanks to active hormonal preparations, climacteric disease soon ends in cure. The abnormal secondary neuro-endocrine reactions disappear and the psychic state is improved. These hormones stand in the same relation to the climacteric disease as insulin to diabetes.

On the whole, two or three years must be allowed for the climacteric storm.

Therapeutics. Psychotherapy plays a preponderant role, and is less the psychotherapy of the psychoanalyst than that of the endocrinologist. The mental conflicts which have brought about imbalance of the mind must be adjusted, and this rectification has not merely a psychological effect but also

contributes to adjustment of the neuro-endocrine systems. The patient must be taught to take a right attitude towards the cessation of sexual life, to see things as they are, and to cultivate a philosophical outlook. It is important to impress upon these women that life is not finished. Modern methods of treatment succeed in compensating the severe trials imposed by the climacteric disease—the obesity, the wrinkles, the fatigue, the various organic lesions. Menopausal women can be made to appear, if not younger, at all events physically well, and psychotherapy adds to this the serenity so well expressed by Michelet: "The autumn of life is a time full of mystery, of all that is unperturbed. It resembles a wide plateau on a mountain top, swept by a fresh breeze beneath a fair and cloudless sky, whence the earth is contemplated with equal serenity by night and by day. It is the stage of recollection and most sincere happiness." There is probably no neuro-endocrine disease, with the exception of Graves' disease, in which psychotherapy is more effective. Before the era of endocrinotherapy great physicians treated women with climacteric disease successfully thanks to their understanding of human nature, and nowadays appropriate psychotherapeutic handling adds its potent action to that of endocrinotherapy.

Diet needs regulation according to the individual factors. In general it should be of low protein, fat and carbohydrate content and rich in vitamins. Constipation should receive careful attention.

Endocrinotherapy is a basic procedure. It should be remembered, however, that in female climacteric disease there can occur a phase of hyperœstrinism followed by a phase in which hyperproduction of pituitary gonadotropic predominates. In the absence of urinary hormonal determination œstrogens should be given first but with care. If they are tolerated, and still more if improvement is apparent (showing that the patient is not in the phase of hyperœstrinism) the dosage can be increased considerably but always under careful supervision. They can be implanted in pellets. Œstrogen acts through its depressant action on the anterior pituitary, whose hyperfunction is the most important element of climacteric disease. As a rough plan 5 to 10 milligrams of œstradiol benzoate can be given in injection or by mouth twice weekly. The new synthetic œstrogens of stilbœstrol type are valuable because very active orally. Progestin also has an antepituitary sedative action and in my experience has often proved superior to œstradiol, especially as it can be used in all cases. Male hormone preparations can be used for the same purpose. For some inexplicable reason they often succeed where œstrogen has failed. Their administration, however, must be carefully supervised.

Vitamin E gives excellent results, particularly for vasomotor flushes, and should be used alternatively or even in preference to œstrogens. Ten to twenty milligrams daily of tocophenol for one to three weeks are advised.

Other medicines are valuable as adjuvants. Biological sedatives such as cratægus and passiflora are often indicated. I have obtained excellent results from the homœopathic drug lachesis given according to its special indications.

Physical procedures are valuable adjuvants. Ultra-violet irradiation does not seem to give the same good results as in the other hypo-ovarisms, but tepid

douches are useful and high altitude climates more effective than in the other hypo-ovarisms. Short waves, infra-red and massage are indicated for the very frequent rheumatic manifestations, foam baths for the obesity. As I have often noted at St. John's, these physical methods are often sufficient for the cure of most cases of female climacteric disease. Spas such as St. Moritz, Royat and Bagnoles are the best resorts for these conditions. St. Moritz, however, is contraindicated for women with very high blood pressure, although beneficial in mild hyperpiesia. Royat and Bagnoles are indicated when circulatory disturbances dominate. Auto-hæmotherapy, which I have followed Abrami in using, is often an excellent measure.

CHAPTER XXVI

CONSTITUTIONAL DYSMENORRHŒA

(PRIMARY DYSMENORRHŒA)

Physiopathology. Constitutional dysmenorrhœa is determined not by a local genital factor but by a disturbance in the system of constitutional regulation. It is often described as primary dysmenorrhœa, and although both terms are used in this work constitutional dysmenorrhœa seems more accurate. It is a disease for which the endocrinologist is often consulted.

Pain in dysmenorrhœa arises from uterine contractions, and is due either to normal contractions felt intensely or to abnormally strong contractions. In constitutional dysmenorrhœa either the constitutional regulators of general sensitivity or those of uterine motility are disturbed.

It is probable that a lowering of the sensory threshold is the primary element in constitutional dysmenorrhœa. Sensations from the viscera and thus from the uterus follow sensory fibres which at first lie in the tracts of the sympathetic and parasympathetic nerves of the viscera but later separate and follow the general sensory tracts. Thus they go first to the thalamus, where they are felt in a low state of elaboration, and then to the cortex where they are progressively more delicately elaborated, first in the sensory cortex, next in the psychosensory and finally in the psychoassociational cortex. The lowering of the sensory threshold may be due to an abnormal state of the peripheral sensory nerves, which begin in highly specialised sensory nerve corpuscles situated in the myometrium, follow the superior hypogastric plexus (the so-called pre-sacral nerve), connect with the inferior lumbar sensory ganglia and then reach the medulla, where they follow the spinothalamic tracts up to the thalamus. This abnormality of the peripheral sensory uterine nerves is accepted by Davis on the basis of his surgical results and anatomical findings

of neuritis. But the histological picture of this " neuritis " is not clear, and the surgical results do not need this " neuritic " explanation. The lowering of the threshold for uterine sensory stimuli is more adequately explained by an abnormal reactivity of all the uterine sensory centres, spinal, ganglionic, thalamic, cortical, bound up with a special constitutional structure.

In this structure a psychological disturbance, an abnormal mode of function of the psychoassociational cortex, dominates. This is clinically distinct in the special personality features of the dysmenorrhœic woman.

Other disturbances of constitutional regulators are associated with this basic psychological constitutional disturbance. The sympathetic system is in hyperfunction. Hypothyroidism and hyperœstrinism are frequent. All these disturbances of psychoassociational cortex, sympathetic, thyroid and œstrin systems act in combination as a complete disturbance of the constitutional regulatory system of forces to maintain an abnormal reactivity of the nervous centres in which uterine sensory stimuli are received and elaborated.

The sympathetic nervous and endocrine disturbances can act also by intensifying uterine contractions and by producing abnormal uterine contractions or spasms. Œstrin and pituitary oxytocin (postpituitrin) stimulate uterine motility. Thyroxin sensitises the uterus to the contractile action of oxytocin. The sympathetic system also stimulates uterine contraction. On the contrary, progestin and the parasympathetic system inhibit this contraction. The parathyroids, by maintaining normal calcæmia and thus normal neuro-muscular irritability, may play a certain role, parathyroid hypofunction and thus hypocalcæmia thus being a factor of increased uterine neuro-muscular irritability.

Constitutional or primary dysmenorrhœa is not a mental, an endocrine or a neuro-vegetative disease. Like any other constitutional disease, it is a particular modality of imbalance of the whole system of constitutional regulation. The object of the clinician is to discover the modality of the imbalance without concentrating on any particular component of the system of constitutional regulation.

Etiology. The predominant etiological factor is a special personality, a particular biotype centred on an abnormal reactivity of the sensory centres which receive sensory stimuli from the uterine muscles.

Physically the patient is a more or less typical eunuchoid, tall, asthenic, thin, flat-chested, with tendency to visceroptosis. The uterus is hypoplastic, often anteflexed. Neither the hypoplasia nor the anteflexion is a cause of the dysmenorrhœa; both are simply stigmata, biotypological features of women prone to dysmenorrhœa. In fact, many women with a hypoplastic uterus have no dysmenorrhœa. The reactivity indicates an abnormal lability of the autonomic system. There is easy flushing, tachycardia, perspiration and various allergic manifestations such as asthma, urticaria and migraine. There is also a distinct tendency to visceral, mainly digestive, spasticity. Mentally the patient is highly strung, highly sensitive, alert, apprehensive, self-centred.

Certain environmental factors act on this biotype to accentuate the hypersensitivity and direct it to the uterus. Such individuals have usually been coddled and over-indulged in childhood by their mothers, perhaps themselves dysmenorrhœic. They learn to centre their attention on menstruation and are advised to avoid any exertion and even to rest during their periods.

Symptomatology. There is a history of progressive menstrual pain which has its inception at the first or second menstruation or occurs for the first time after a few months or years of painless menstruation.

The pain is intermittent, sharp, colicky. It is usually limited to the lower abdomen but often radiates to the back and thighs. In some cases the back pain is predominant. It is relieved by rest, lying down and hot fomentations. It is accompanied in some cases by general nervousness, nausea, vomiting, bradycardia, the last three being vagotonic manifestations.

In one class of case it begins one day, or a few days, before menstruation, and may be accompanied by the syndrome of pre-menstrual tension, nervousness, swelling of the breasts, headache and other nervous manifestations, all these symptoms as well as the pain disappearing with the flow. In another series of cases pain occurs with the onset of bleeding, reaches its maximum intensity in 24 hours and thereafter diminishes progressively.

The pain may occur at every menstruation or only at some periods. Its intensity may vary in successive menstruations. It diminishes or disappears on marriage, although less frequently than is popularly believed, after pregnancy, with treatment or with the passing of years.

The flow varies. It may be scanty. In other cases it is abundant with clots, indicating some retention of blood in the uterus. There are some rare cases in which membranes are passed with the flow, constituting pseudo-membranous dysmenorrhœa.

Primary dysmenorrhœa should be differentiated from uterine pain accompanying chronic pelvic inflammatory disease, intra-mural fibroids or endometriosis. This last case offers the greatest difficulty because, as in primary dysmenorrhœa, often no definite genital lesion is encountered. The aberrant endometrium may be in the ovary, the recto-vaginal septum, the rectum of the myometrium. It undergoes cyclic changes, bleeding and desquamation just as the normally situated endometrium. In ovarian endometriosis pain is usually unilateral, occurring before the onset of bleeding, and an ovarian mass may be detected. In recto-vaginal and rectal endometriosis nodules or tumour are perceptible to the examining finger. In myometrial endometriosis diagnosis is more difficult and is usually not made before operation for " intractable dysmenorrhœa."

Pre-menstrual pain occurring with sclerocystic ovaries should also be differentiated from primary dysmenorrhœa. Physiopathologically it represents a borderline condition. Sclerocystic ovaries are due to hyperœstrinism which is a factor in primary dysmenorrhœa, and many patients operated on for primary dysmenorrhœa show sclerocystic ovaries. Practically, however,

this differentiation should be made. Pain here is usually pre-menstrual and rarely persists after the onset of the flow. This is called ovarian dysmenorrhœa. It is unilateral or bilateral but always confined to the lower abdomen and less diffuse than in primary dysmenorrhœa. It is not associated with bladder irritability.

Therapeutics. As the condition is a constitutional disease it should be attacked by the procedures of constitutional medicine. This seems to be the opinion of gynæcologists, and is voiced by Novak in the following words. "The intelligent treatment of this disorder can never be restricted to the pelvis alone and must include a thorough study which may carry the physician far afield into the domain of internal medicine, endocrinology, psychiatry and other branches of clinical investigation."

Psychotherapy should be considered first. The confidence of the patient must be gained, her conflicts must be solved, and she must be re-educated as to the significance of menstruation while being treated by more organic methods. It should be remembered that dysmenorrhœa may be a manifestation of anxiety neurosis or more severe psychoneuroses. In his psychotherapeutic handling the internist will stress investigation and correction, if necessary, of sexual habits and reactions, since sexual excitement without relief such as occurs in long engagements, coitus interruptus and masturbation may determine or aggravate dysmenorrhœa through the pelvic congestion they determine.

Physical and dietetic measures have next to be considered. Outdoor exercise is advocated for those whose muscular tone is poor. Sports and outdoor activities should be continued if possible during menstruation. The correction of faulty posture is necessary. High altitude climates and certain thermal baths are beneficial. Diet should be liberal with well-balanced vitamins and calcium. Disturbances of digestion and intestinal elimination must be corrected.

Tonics and sedatives are constitutional medicines to be administered according to indications. Calcium is often indicated per os or in injection. Iron is necessary for anæmic women with constitutional dysmenorrhœa. Of the nervous sedatives I prefer, for prolonged treatment, certain homœopathic preparations such as ignatia, tincture of cratægus and passiflora. Bellergal given in the days preceding menstruation and during menstruation has shown good results.

Endocrinotherapy is a very good adjuvant. Thyroid gives brilliant results in cases with hypothyroidism. Progestin, chorionic gonadotropin and testosterone administered in the premenstruum are helpful but their effects are not permanent. Œstrogens are indicated as helpful although not highly successful in cases of hypoplastic uterus. In my opinion insulin is the best agent. It acts particularly but not exclusively on patients whose nutrition is poor. Its effects are due not only to the improvement of nutrition but principally to some unknown favourable and lasting influence on ovarian function. 10–15 units once daily before the mid-day meal often brings lasting relief to under-weight visceroptotic women.

Special care is needed for treatment of the attack of dysmenorrhœa. Rest is not absolutely necessary except when pain is severe. This pain must be relieved. The internist has a choice of atropine, benzyl benzoate and bellergal. In mild cases sedatives of the aspirin and veganin type and in severe cases opium tincture are indicated.

Local surgical treatment is for consideration only in intractable cases. It may do harm by concentrating the attention of the patient on her uterus. This is especially true of the tampons used by the " medical gynæcologists " for such patients many years ago.

Dilatation of the cervix, based on an exploded physiopathological conception, is a hit-or-miss procedure. I have seen it miss much more frequently than hit, and in the rare cases where it succeeded the result might have been due to a psychological or " shock " effect procurable by simpler methods. It is true that dysmenorrhœa is often cured after pregnancy, but whether the cure is due to the cervical dilatation caused by delivery is problematic, as so many neurohormonal changes take place during pregnancy. Resection of the pre-sacral nerve calls for more serious consideration, and although Cotte, who introduced this method, appears too optimistic, the statistics of Davis, who has performed the operation extensively in this country, point impressively to 75 per cent. of success. It is a major operation and thus indicated only in really intractable cases.

Other procedures are the injection of alcohol into the plexus of Frankenhaüser, which requires highly specialised expertness and thorough and prolonged dilation of the cervix by means of the Hirst metranoika advocated by Mazer and Israel. This probably cures through pressure desensitisation of the nerve fibres of the lower uterine segments.

CHAPTER XXVII

PREMENSTRUAL TENSION

Premenstrual tension is a disease characterised clinically by a train of symptoms appearing during the real pre-menstruum and vanishing abruptly with the onset of the flow, and by similar symptoms at the intermenstruum. Physiopathologically it is characterised by hyperœstrinism or hypoprogestinism. The condition has been studied principally by Frank.

Hyperœstrinism is considered the essential physiopathological basis of premenstrual tension. This is demonstrated by the occurrence of the clinical manifestations during the œstrin peaks (the intermenstrual or ovulation peak and the premenstrual peak), by certain hormonic studies indicating high œstrogens in the blood and urine, and by the prompt action of the œstrin antagonist, progestin. Many of the symptoms, including ulcerative stomatitis,

have been reproduced by œstrin injections given for conditions unrelated to premenstrual tension.

According to Greenhill and Freed, hyperœstrinism acts by causing retention of sodium in the different tissues of the body and thus œdema of the brain or gut and other affected organs. They support their view by the prompt action of ammonium chloride, but careful tests of water and salt balance in these patients fail to confirm it.

Over-production of postpituitary anti-diuretin probably plays a certain role and may occur through the œstrin stimulus. Edeikin and Griffith found an appreciable increase of the anti-diuretic hormone in the blood of a woman with mitral stenosis who repeatedly developed premenstrual pulmonary œdema. They treated their patient successfully with pituitary irradiation, a procedure which lacks physiopathological significance, however, as röntgen irradiation of the pituitary can act also on the gonadotropic secretion.

These endocrinisms constitute only part of the physiopathology of premenstrual tension. The other part is formed of the particular tissue and organ reactivity, due to genetic or acquired factors, through which the hormonic disturbance is enabled to localise its effects on a special tissue or organ.

Clinical History. Personality changes occur during the ten or fifteen days before the onset of menstruation and end abruptly with the flow. Nervous tension is noted, manifested by restlessness, inability to concentrate and irritability, which causes the patient to be annoyed by trifles, unreasonable emotional outbursts, causeless crying spells. In some cases libido is increased, even to the point of premenstrual nymphomania. This is the more remarkable because the sexual urge is usually more intense in women during the œstrin phase of the cycle, *i.e.,* the first fourteen days after the onset of menstruation, than during the progestin phase, *i.e.,* the fourteen days preceding the next menstruation. Here, of course, the œstrin phase seems to be prolonged.

Next come various neurological symptoms, principally insomnia and headache, which in some cases takes the form of migraine (premenstrual migraine). Such patients have a high gonadotropin titre in their urine, although low œstrin. This migraine is of the usual allergic nature but hyperœstrinism (or hypersecretion of *a*-gonadotropin) is an important contributing factor. Backache is nearly constant. In some cases convulsions occur, constituting what has been described as hyperœstrinic epilepsy. Although these convulsions may be under the direct influence of hyperœstrinism, however, they are in most cases manifestations of an organic or allergic epilepsy made manifest by the premenstrual hyperœstrinism. I have even observed a patient with a pancreatic adenoma giving rise to hypoglycæmia, who had convulsive attacks nearly exclusively in the premenstrual as well as the intermenstrual period. Even severe mental disturbances are noted in some cases, these also being manifestations of a psychosis made manifest by hyperœstrinism.

Other more localised organ manifestations are seen during the premenstrual phase, such as asthma, pulmonary œdema (Edeikin and Griffith), ulcerative

stomatitis distinctly cyclic and resisting all forms of treatment (Ziserman), swelling of the salivary glands (Racine) and generalised œdema (Thomas). The breasts swell and feel uncomfortable. Dysmenorrhœic pain may occur in the few days before the flow.

Fever occurs in some cases, usually of low degree. Misdiagnosis as tuberculosis has been frequent. It should be recalled that febrile conditions are often aggravated in the immediate premenstrual period, and that even afebrile tuberculous patients show high temperature during that period.

There is usually but not always excessive œstrin in the urine. Œstrin in fact may be used up and not excreted. Increased *a*-gonadotropin is found in some cases as well as deficient pregnanediol in the urine. In a case described by Hamblen characterised by premenstrual dermatosis, menstrual headache and dysmenorrhœa, an increased excretion of sodium pregnanediol glycuronide (135 instead of 45–55 mg. in the whole menstrual cycle) was found, and œstrogens relieved the condition. This would indicate a hyperprogestinic and not a hyperœstrinic basis for this case of premenstrual tension, but hormonic excretion interpretation is too delicate to allow of any definite conclusions.

All these symptoms disappear immediately the flow begins. In a few cases, however, I have noted great fatigue during menstruation and for some days afterwards, so that these patients were not free of symptoms except for a few days of their cycle.

This represents true premenstrual tension, but in some patients these symptoms, particularly uterine pain, occur during the intermenstruum at the phase of ovulation (the tenth to twelfth day after the onset of bleeding). These cases are designated as of cyclic intermenstrual pain.

Premenstrual tension should be differentiated from primary dysmenorrhœa (these diseases differ physiopathologically, clinically and therapeutically) and from various diseases such as asthma, epilepsy, psychoses, tuberculosis, whose symptoms are simply aggravated in the premenstrual period.

Therapeutics. Constitutional treatment on the lines described for primary dysmenorrhœa is important. Insulin is less effective than in the former disease but progestin is very beneficial. It brings immediate relief, and in some cases serial treatment has a permanent effect. It should be given in the second half of the intermenstruum, starting with 10–20 mg. divided into 2–4 injections. Chorionic gonadotropin is useless, probably because not sufficiently luteinising.

Greenhill and Freed advocate the oral administration of 0·60 gram (10 grains) of ammonium chloride three times daily and the withdrawal of salt during the second half of the menstrual cycle. I have observed good but not permanent results of this method, which at all events is worth trial.

Premenstrual migraine is often relieved by œstrogens (Thomson). It is not illogical to use œstrin in hyperœstrinism, because œstrin inhibits secretion of *a*-gonadotropin and thus may cure hyperœstrinism.

B-complex is often a good adjuvant. Biskind has shown that vitamin B deficiency inhibits the œstrogen-inactivating mechanism of the liver and thus

more active œstrin invades the circulation and causes manifestations of hyper-œstrinism.

CHAPTER XXVIII

FIBROCYSTIC MASTOPATHY

Fibrocystic mastopathy is a disease of the breast characterised anatomo-clinically by the formation of fibrocystic nodules under the influence of an endocrine disturbance, principally hyperœstrinism. It is a crystallised hyper-œstrinism. It is thus a constitutional mastopathy.

The disease, at all events in its advanced phase, was described by Paul Reclus in 1883. Before the work of the great Paris surgeon, my teacher, it was confused with cancerous lesions. Reclus showed it to be a disease *sui generis*, non-malignant, and thus saved many women from unnecessary amputations of the breast. As often occurs when a clinician isolates a disease *sui generis*, subsequent work shows a special physiopathology and etiology, and the endocrine etiology of this disease was discovered recently through the work of Goormatich and Amerlink and of Dean Lewis and Geschikter, who showed the hyperœstrinic nature of the condition.

Physiopathology. The disease results from an excess of hormone, mainly œstrin, acting on breast tissue, which genetically offers special reactivity to this hormone.

The hyperœstrinic factor in fibrocystic mastopathy is demonstrated by (*a*) the experimental production of this disease through œstrin injections in animals (Goormatich and Amerlink); (*b*) the presence of definite causes of hyperœstrinism in women suffering from this disease and of other manifestations of hyperœstrinism. I have recently seen a case in which ovarian endometrioma, discovered at operation, caused dysmenorrhœa, uterine fibromyoma and fibrocystic mastopathy; (*c*) the therapeutic action of the œstrin-antagonistic testosterone. Hormonic studies are not of great help because of the difficulty of interpretation.

Certain authors accept an excessive pituitary mammogenic secretion as a factor in the genesis of fibrocystic mastopathy. Mammogenin is, like œstrin, a normal growth hormone for the breasts, and thus in certain cases could become tumorigenic through excessive action.

The cause of the hyperœstrinism or hypermammogenism is not known. A genetic abnormal lability of the œstrin or mammogenic system is accepted. Psychogenic factors are important in accentuating hyperœstrinism. A more definite factor is found in vitamin B deficiency, Biskind having shown that it causes hypofunction of the liver as regards œstrin inactivation (normally œstrin is inactivated in the liver). Thus an excess of œstrin is in the circulation.

Mazer and Israel indicate a habitual stimulation of the nipples as a factor of fibrocystic mastopathy through reflex hypersecretion of mammogenin, and quote an illustrative case of a woman suffering from this disease. She did not

react to œstrogen, but disclosed that suckling by her husband as a preliminary to intercourse had been routinely practised since marriage. Discontinuation of this practice resulted in permanent cure. It should be remembered that experimentally Selye and McKeown have shown that suckling stimulates the breast of virgin rats to full development and lactation.

Clinical History. The woman who suffers from this disease shows certain special biotypological features. She is usually over 30, nervous and highly strung. Astley Cooper noted long ago that such patients are of an irritable and suggestible nature. This personality feature indicates hyperfunction of the *a*-gonadotropin-œstrin system. She is thin. Fat women rarely show this mastopathy, probably because they are of hypopituitary type. There is no undernutrition, and the general health is good. She is usually childless, or has not been pregnant for five or six years. Menstruation is usually regular, dysmenorrhœa occurring in some cases in connection with the nervous condition of the individuals.

The first phase of the disease is a phase of mastodynia that is characterised essentially by pains in the breast. This is felt for a few days before menstruation and ceases when the flow begins. Progressively the painful days increase until the patient is rarely free from pain any day during the cycle. Menstruation remains regular. The pain varies in intensity, usually passing downwards and radiating to the arms, but is mostly felt in the upper and outer quadrant of the breast. It worries the patient and causes great fear of cancer. On palpation the pain is accentuated, the most painful tissue being usually the upper and outer quadrant. The breasts appear larger, they transilluminate poorly, and granular and nodular areas of increased density are found. Anatomically the breasts show clusters of terminal tubules surrounded by increased amounts of connective tissue but without any lobular formation. The disease at this phase can retrocede spontaneously or following treatment, or can be arrested more or less at this phase, or can pass into the following stage.

The second phase is called the phase of adenosis. It begins in the late thirties or the early forties, is characterised anatomically by an epithelial proliferation which results in small intracystic papillomas or non-encapsulated adenomas. As in the previous phase, symptoms are bilateral, although predominantly in one breast. The spontaneous pain as well as the pain on palpation is less intense than in the first phase. The breasts are usually of fair size, with considerable parenchyma, but later, when the stroma of the breasts increases in density, the size of the breast is reduced. The gland shows a saucer-like or liver-like edge. On palpation in the beginning, multiple indefinite nodules or small shotty masses are felt in one or both breasts, usually distributed about the periphery. Later, areas of increased density are perceived and discrete multiple tumours. A dark bloody discharge from the nipple is seen in 7 per cent. of cases (Lewis and Geschickter). The general health continues to be good but menstruation is often disturbed, with pain, irregularity and shortened cycle. At this phase the disease can recede spontaneously or following treatment, pregnancy or the menopause. It can be arrested at this

stage or can pass into the third stage.

The third phase is characterised by cyst formation. It occurs in the late forties towards or during the menopause. Patients can be seen for the first time at this phase, the other two stages having been more or less latent. The ducts dilate, coalesce and form cysts, and into these cysts papillomatous processes may project. The interstitial fibrous tissue is increased and infiltration of small round cells is noted. Cysts make their appearance very quickly and may reach an appreciable size, approximating that of a mandarin orange. Often only one cyst is detected, although the rest of the breast and the opposite breast are shotty and fibrous and show some smaller nodules. The cyst is round, smooth, freely movable. It transilluminates clearly, and on aspiration a cloudy milk-like fluid is obtained. The cysts may disappear spontaneously but usually remain, showing changes in their volume.

Certain authors accept as a terminal phase cancerous degeneration, but in the light of most clinical reports, and in conformity with my own experience, cancerous degeneration, if indeed it ever occurs, is exceptional. It is not considered a pre-cancerous lesion (J. C. Bloodgood), and if cancer occurs it is coincidence. A careful following up, however, is necessary.

Therapeutics. Careful diagnosis is necessary. If there is any doubt the nodule or cyst should be excised and examined microscopically. Certain large cysts should be removed, but on the whole treatment is essentially internistic. Constitutional treatment on the lines described for dysmenorrhœa should be applied.

Testosterone injections, in my opinion, constitute the best therapeutic method, and fine results can be achieved by a skilful endocrinologist. Desmarets and Capitaine were the first to use this method on a large scale. Fairly high doses are needed, and should be given mainly at the œstrin peaks, the ovulation phase and the immediate premenstrual period.

Lewis and Geschickter give œstrin in high doses and have obtained good results, particularly in the early phases. In high dosage œstrin inhibits antepituitary secretion of *a*-gonadotropin and thus causes hypo-œstrinism. It may act also by inhibiting mammogenic secretion. Small doses are to be avoided. Although the carcinogenetic action of œstrin occurs only with very high and prolonged doses, one hesitates to use this method.

B vitamin has its indications here also, as in all cases of hyperœstrinism.

CHAPTER XXIX

METROPATHIA HÆMORRHAGICA

(" FUNCTIONAL BLEEDING ")

This is a disease characterised by hæmorrhage from the uterus determined by a rupture of the hormonal balance which maintains the normal " bleeding " functions of the uterine mucosa and in general the normal vascularisation of this mucosa. A local factor depending on the enzymes of the endometrial

cells intervenes. It is a very common and tiresome condition for which the endocrinologist is often consulted.

Primary Ovarian Hyperœstrinic Metrorrhagia.

This metrorrhagia is linked with a granulosa tumour of the ovaries. The mechanism of action is the œstrin hypersecretion of the tumour, and the condition is thus an ovarian hyperœstrinism.

Granulosa tumours of the ovary are relatively rare (in 1935, Bland and Godstein collected 245 cases). They vary in size from small microscopic nodules to a growth 15–20 cm. in diameter. They are usually but not always unilateral, and are composed of granulosa type cells. They possess a low degrees of malignity. When they occur before puberty (a rare occurrence) they give rise to pubertas præcox. When they occur after puberty they determine through their œstrin hypersecretion an endometrial hyperplasia which gives rise to the syndrome of metropathia hæmorrhagica. This is similar to that of cystic glandular hyperplasia of the endometrium and will be described with it. Exceptionally, other forms of ovarian tumour give rise to metropathia hæmorrhagica.

Treatment of this form consists in removal of the tumour.

Cerebro-Pituitary Hyperœstrinic Metrorrhagia.

The physiopathological basis of this condition is a total hyperfunction of the œstrin system beginning at the diencephalon. The intense diencephalic drive induces intensive secretion of *a*-gonadotropin, and this in its turn stimulates to excess the œstrin-secreting ovarian follicles. This intensive stimulation disturbs the evolution of the follicles. They fail to rupture (the rupture of Graafian follicles demands a definite balance of *a* and *β* gonadotropins). They increase in size, become cysts, and their œstrin secretion is intensified.

The excessive œstrin secretion determines changes in the endometrium known as cystic glandular hyperplasia of the endometrium. This constitutes an exaggeration of the œstrin-endometrium, *i.e.*, of the proliferative endometrium. The glands are long, coarse and irregular, and often show cystic dilatation. The epithelium is very irregular, and epithelial cells are often heaped in irregular rows. Macroscopically the endometrium is thickened and velvety. Its surface is thrown up into folds and polypoid protrusions (hence the old name of endometritis fungosa) and studded with small cysts. The endometrial cycle is also disturbed, and the endometrium never passes into a a secretory phase because the excessive *a*-gonadotropin-œstrin function inhibits the *β*-gonadotropin-progestin function. When bleeding occurs at all it proceeds from a proliferative and not, as normally, from a secretory or progestational endometrium. It occurs probably from blood vessels opened by the sloughing of necrotic areas; however, nothing is known of this mechanism of bleeding because in fact nothing is known of the mechanism of normal uterine menstrual bleeding.

The disease can be encountered at all ages after puberty but is more frequent after 30.

It is manifested first by a phase of amenorrhœa. After a number of more or less regular periods menstruation stops. The duration of the amenorrhœa varies. It may be very short, almost imperceptible, and the disease may be considered to start by attacks of uterine bleeding. In other cases amenorrhœa is prolonged for months.

Next comes a phase of cyclical menorrhagia. The patient seems to have a prolonged and intense menstruation but, as endometrial biopsy can show, the bleeding is not true menstruation but a flow of blood from an anovulatory proliferative endometrium.

Progressively the condition passes into a phase of attacks of metrorrhagia with intervals of amenorrhœa. The cyclical character of the bleeding is lost. It becomes more frequent and more prolonged, or rarer but equally prolonged. In the intervals between real bleeding there is oozing, which is much more troublesome and debilitating. When metrorrhagia is abundant clots may be passed. The intervals between attacks of bleeding may be very long, amounting to new phases of amenorrhœa lasting for months.

Various concomitant symptoms are noted, and are due to the debilitating anæmia. Dysmenorrhœa is absent, an important fact as hyperœstrinism is considered by many authors to be a preponderant factor of dysmenorrhœa. However, other manifestations of hyperœstrinism such as premenstrual tension and a neurotic highly strung personality may be present.

The biochemical findings are not striking except that despite the physiopathological conception, excessive œstrin is not detected in the blood or urine. As has been remarked previously, the latter finding is unimportant because it is possible that the endometrium fixes œstrin.

The course of the disease varies. It often retrocedes spontaneously, as in the forms occurring at puberty. In other cases intervention is necessary. Curettage was the only treatment until a few years ago. To-day endocrinotherapy is used. Notwithstanding the carcinogenetic role of œstrin in certain biological experiments metropathia hæmorrhagica never degenerates into cancer.

Formes frustes of this disease are very numerous. In these the typical sequence of amenorrhœa, menorrhagia, irregular metrorrhagia interrupted by phases of amenorrhœa does not occur, and the endometrium does not show the typical histological findings described. In many of these forms the only symptom is undue prolongation of the menstrual period, *i.e.*, an intense menorrhagia. In others, irregular prolonged metrorrhagias occur after a comparatively short phase of amenorrhœa. Often these cases improve spontaneously. Many " functional bleedings of puberty " are formes frustes of constitutional cerebro-pituitary metrorrhagia and are due to the endocrine storm of puberty. Many of the " functional bleedings of menopausis " are of the same nature.

Precise gynæcological diagnosis is necessary in this condition, and no endocrinologist should attempt to treat such cases without previous investigation by a gynæcologist. Differential diagnosis must embrace polyps, submucous

myoma, carcinoma of the uterus, incomplete abortion and endometritis, especially post-abortion endometritis. This examination can be avoided only for young girls with slight temporary menorrhagia. Diagnostic curettage should be the rule for patients over 30, particularly if they are of metrorrhagic nature. In fact, biopsy of the endometrium, which is now of so simple a technique, should be in general use.

Therapeutics. Treatment is for most cases essentially endocrinological. Thyroid, œstrin and progestin are used. Thyroid seems to be one of the most important agents, particularly in the constitutional metrorrhagias of puberty and can be pushed to tolerance. It acts through an unknown mechanism because patients whom it benefits do not show symptoms of hypothyroidism and may have a normal metabolic rate. Œstrin administration in some cases is a good method and acts probably by blocking *a*-gonadotropin secretion and thus by inhibiting œstrin secretion. This interpretation is not wholly satisfactory but good results appear numerous, and the hesitation justified in fibrocystic mastopathy and based on the carcinogenetic action of œstrin can be set aside. Despite the relatively high doses of œstrin there is no noxious action on the ovaries. Patients treated by McGinn with this method have later become pregnant.

Next comes progestin. It usually gives only symptomatic relief but is a good simple method of tiding over a difficult period. It may in certain cases, however, cause aggravation. Chorionic gonadotropin has similar indications. Equine gonadotropin has given very meagre results. Synapoidin, a combination of β-gonado-stimulin and a pituitary synergist, has not yet been thoroughly studied.

Testosterone should be avoided as much as possible. It checks bleeding but may upset the endocrine balance.

A good technique for œstrin administration in combination with progesterone is indicated by McGinn. (*a*) During the first 15 days diethyl stilbœstrol (5–10 mg.) to be taken at night before retiring, in a glass of milk. Bleeding stops in 5–10 days but treatment continues until the 15th day. (*b*) Interruption of treatment. Bleeding occurs after 5–9 days. It is a withdrawal bleeding, and is therefore of no import in the treatment. It stops, and in two or three weeks a regular menstruation occurs. (*c*) After the first regular menstruation, 3 mg. of diethyl stilbœstrol are taken on the 10th, 11th, 12th and 13th days of the cycle. 10 mg. of anhydroxyprogesterone are taken daily from the 14th to the 24th day of the cycle, but stopped before the 24th day if bleeding occurs.

Vitamin B complex is a valuable adjuvant. It acts probably in cases of hyperœstrinism due to liver insufficiency and thus to defective liver neutralisation of œstrin. Certain liver preparations probably act through the same mechanism.

General constitutional methods are necessary here as in all endocrinopathies. Iron in strong doses should be given against anæmia.

Because of the recognised controlling influence of the spleen in

hæmorrhage, röntgen rays have been applied in the spleen with good results. Pituitary radiotherapy is of more delicate application, and as it can damage the pituitary it should be avoided.

Curettage is indicated in intractable cases. Results are erratic. Ovariectomy or irradiation of the ovaries can be tried in the last resort.

Thyroid Metrorrhagia.

Many metrorrhagias are determined by hypothyroidism of varying clinical degree. Such a diagnosis should always be considered in the various "functional bleedings." The hypothyroidism giving rise to metrorrhagia is often a forme fruste or the form with nervousness. It should be remembered that for some unknown reason thyroid benefits non-hypothyroidean metrorrhagias.

CHAPTER XXX

ENDOCRINE METABOLIC FACTORS IN FEMALE INFERTILITY

In the treatment of both female and male infertility, and thus in the correction of sterility, the role of the endocrinologist is preponderant. It is one of the most frequent tasks of the endocrinologist, and is therefore described in detail.

It has been computed that about one in eight marriages is barren. This barrenness is due to female infertility in 75 per cent. of cases. It is unnecessary to point out that sterility ranks high among the causes of unhappiness in marriage, because in a childless marriage the strongest of all cementing forces is lacking. Apart from individual considerations, social factors are important in view of the falling birth rate in countries of high civilisation.

In female infertility two aspects need to be distinguished; the inability to conceive, and the inability to bear live offspring, *i.e.*, absolute sterility and relative sterility respectively. Both incapacities are considered in this chapter because they share the same basic physiopathological mechanism and the same clinical result, inability to bear offspring.

Female infertility depends not only on the special make up of the woman but also on her mate. A woman of low fertility will manifest infertility if married to a man of low fertility and their marriage will be barren, but if she afterwards marries a man of high fertility she may prove herself fertile. Thus infertility is frequently relative for each individual because it depends to some degree on the partner.

Physiopathology. Physiopathologically a woman is infertile because any one or more of the four factors of her part in reproduction ovoproduction, tubal transport and fertilisation, vagino-uterine reception, uterine fixation of the embryo are disturbed. The mechanism of these four factors shall be considered.

I. *Ovoproduction.* This consists in formation of the Graafian follicle, development of that follicle, bursting of the Graafian follicle and thus liberation of the ovum, the last phase being described principally as ovulation.

The Graafian follicles form during intra-uterine life by ingrowth of the surface cells of the ovary. There are 400,000 follicles at birth, undeveloped, primordial follicles. Most of them retrocede and become atretic, and at puberty about 35,000 remain. No new follicles are produced after birth. The formation of Graafian follicles is regulated by the primordial incretory organs, the genes and organisers.

The Graafian follicles mature during and after puberty. During this process the ovum, which is enclosed in the follicle (the egg chamber), assumes an excentric position and develops, becoming the largest cell in the body. At the same time the other cells in the follicle proliferate and the ovum becomes completely surrounded by a mass of proliferating granulosa cells. The quantity of follicular fluid steadily increases, raising the intra-follicular tension. The Graafian follicle rises to the surface of the ovary, following the path made by a wedge-shaped proliferation of the cells of the outer zone of the granulosa. This proliferative phase of the follicle is at first dependent on the influence of the genes and organisers and soon comes under the control of *a*-gonadotropin (F.S.H.).

Next the matured follicle ruptures, *i.e.*, ovulation occurs. In humans this takes place at about the 10th–12th days of the menstrual cycle, but there are wide variations. The tense follicle compresses the blood vessels of the ovarian surface above. The area becomes thin and avascular, forming the stigma, which eventually perforates and the ovum is discharged. Possibly contractions of the muscular fibre of the ovaries takes part in this process.

Ovulation is under genetic and neuro-hormonal control. Genetic control directing the self-regulation of the cells of the follicle exists at onset. The neuro-hormonal control exists in a special balance of *a* and *β* gonadotropins (F.S.H. and L.S.H.), as has been demonstrated experimentally by production of ovulation following pituitary implants in immature mice (Smith and Engle, 1927), following injections of pituitary extract in the hypophysectomised animal (Hill and Parkes, 1931) and following injections of both *a*-gonadotropin (extracted from castrate urine) and *β*-gonadotropin (extracted from pregnancy urine) whereas *a*-gonadotropin alone does not cause ovulation (Leonard and Smith, 1934).

II. *Ovotransportation and fertilisation.* After discharge the ovum passes first into the ovariotubal hiatus and then into the tube. The ovariotubal hiatus (Meaker, 1934) is the gap separating ovary from tube. In certain animals it does not exist, but a bursa, a peritoneal sacculation, is formed enclosing the ovary and leading to the infundibulum of the tube. In humans the hiatus exists instead of the sacculation, and another mechanism permits transport of the discharged ovum from the ovary to the tube. The egg escaping from the ovary is not in a vacant space. It glides in a thin film of moisture between the smooth surface of the organs in the region of the ovary. The

open funnel of the ovary is directly at hand, and moreover the moisture in which the egg drifts is drawn into the oviducts by the action of the cilia. It is even possible for the ovum to drift across from one ovary to the opposite oviduct, and thus a woman who has had one ovary and the opposite tube removed is not necessarily sterile.

Thus the ovum enters the tube. It progresses downwards through the action of the cilia of the cells lining the tube, but more probably through the muscular contractions of the tube, which move it, according to Corner's description, by a sort of "milking" process. While the ovum descends the sperm coming from the uterus ascends. The two meet, and fertilisation occurs. The journey of the sperm from the vagina to the tube takes only a few hours. The fertilised ovum continues its descent towards the uterus, which it reaches about the fourth day after it has left the ovary as an unfertilised ovum. These four days are essentially tubal days, time itself being unimportant in the passage from ovary to tube. At this stage the embryo is at least in the four cell stage. This tubal phase is important not only as a meeting place between semen and ovum, but also, according to Corner, because it holds back the fertilised ovum until the uterus is ready for it.

The tubal phase is under hormonal and neuro-visceral control. The hormonal control consists in a balance between œstrin, which stimulates tubal movements, and progestin, which inhibits them. The importance of this balance has been shown experimentally. Strong doses of œstrin accelerate the passage of the ovum through the tubes (Whitney and Burdick). Smaller doses prevent the descent of the ovum, locking it (Burdick and Pincus). Injections of posterior pituitary hormones also modify the movements of the muscular fibres of the tubes. The neurovisceral control is effected by sympathetic branches to the tubes, motor in nature and parasympathetic inhibitors.

III. *Vagino-uterine semen reception.* This is an important factor, of which disturbance may lead to infertility. Thus the phenomena occurring immediately after coitus must be considered. There are discrepancies about this part of reproductive physiology, and I give the view which appears to me to be best for working purposes. I have adopted many of the ideas of Kurzrock.

The vagina is highly acid but the cervix is plugged with an alkaline wick of mucus. The slightly alkaline semen penetrates the vagina and according to Kurzrock the variations in *p*H between vaginal walls, cervical plug and semen form an electrical system. The plug forms the positive pole, the vaginal walls the negative, and the negative-charged sperm is thus repelled by the vaginal wall and attracted towards the positive cervix. Thus the sperm travels rapidly towards the cervix. Speedy travel is essential, otherwise the lactic acid continuously produced by the vaginal walls would immobilise the alkaline sperm. Once at the cervix the sperm dissolves the plug through a lytic enzyme it secretes, and penetrates into the uterus about four hours after coitus. Only 20–40 per cent. of spermatozoa penetrate, the loss being due to the necessity of surmounting the barriers of the highly acid vagina and the highly viscous cervical mucus. After penetrating into the uterus the sperm is

directed towards the external os of the tube. This is effected through the motility of the spermatozoa, but their guide to the tubal stoma is not known. At all events, the uterus relaxes, probably because of a specific concentration of acetylcholine in the sperm and its derivatives. Consequently the tubo-uterine sphincters open to allow the sperm to pass through them and begin its tubal ascent to meet the descending unfertilised ovum. Meeting and fertilisation occur, and the fertilised ovum descends. The time factor is important. If the motion of the spermatozoa is prolonged their fertilising power is seriously impaired. If the ovum is not fertilised a few hours after ovulation in the rabbit, it degenerates in the Fallopian tube and is absorbed.

The above delineation is somewhat dogmatic because there are many discussed and unknown factors. It is sufficient, however, to indicate the extreme complexity and delicacy of this mechanism. As in a very precise chronometer, any slight disturbance can upset the entire mechanism. If the vaginal wall, the cervical mucus or the semen has not the optimum *p*H, the sperm is not directed in time to the cervix. If the cervical mucus is abnormally thick, as occurs in some hypoplastic uteri, and if the semen has not its optimum enzyme-producing power, the cervical os cannot be traversed. If the uterus does not relax properly after the sperm has penetrated into its cavity the tubal stoma fails to open and the spermatozoa degenerate in the uterus. Also involved are the unknown factors directing the semen to the tube, the motile power of the spermatozoa and the motor functions of the tubes.

All these mechanisms are under the control of the constitutional regulatory system, particularly that of the neuro-hormonal and neuro-visceral systems. The hormonal system controls vaginal metabolism and thus vaginal *p*H. It controls also the constitution of the cervical mucus. Whereas for the greater part of the month the secretion of the cervical canal is thick, viscid and opaque, at the time of ovulation and in the immediate premenstruum (periods of œstrin rises) it becomes thin, glairy, translucent. The *p*H reaches an average of 8·5, mucin and glycogen increase. Hormones also control the metabolism of the endometrium and thus promote production of a slightly alkaline mucus within the uterus favourable to the vitality of spermatozoa. The experimental production of antisperm antibodies, spermatotoxins, may indicate the possibility of such a factor in certain endocrine metabolic disturbances. The neuro-visceral system controls uterine and tubal motility. Œstrin, progestin intervene principally, but they are not the sole factors.

IV. *Uterine fixation of the fertilised ovum.* The fourth factor and last act in reproduction is the fixation of the embryo in the uterine wall. It is the beginning of the longest act of the drama of reproduction (Corner). As already stated, the fertilised ovum passes into the uterus during the fourth day after ovulation. For the first few days after arrival in the uterus it is free and unattached, and nourished by the secretions of the endometrium, which is modifying into the secretory phase immediately after ovulation. Attachment or implantation starts about the seventh day.

This factor in reproduction is under hormonic, *i.e.*, progestin, influence,

as well as vitamin E control. Other hormonal factors probably intervene for maintenance of normal endometrial metabolism. For example, Zondek finds in 18·4 per cent. of all cases of sterility that the endometrial cells lack glycogen, which characterises them during the progestin phase of the cycle. Normal glycogen storage of the uterine cells and the glycopenia met in sterility are under hormonal influence, and glycogen participates in the nutrition and fixation of the embryo.

Gynæcological Investigation and Treatment of the Sterile Woman.

A short delineation of the gynæcological examination is given to indicate the respective roles of the gynæcologist and endocrinologist. In the first place the gynæcologist has to determine (*a*) whether there is any tubal obstruction; (*b*) whether there is any hostility of cervical secretions (Huhner and other tests); (*c*) whether the woman ovulates (biopsy of the endometrium showing the progestational endometrium when ovulation occurs, and normal or abnormal quantity of pregnanediol glucuronide in the urine).

The following important gynæcological factors should be borne in mind.

Utero-ovarian hypoplasia. The role of this factor is obvious. Hypoplastic ovaries may not produce ova. Hypoplastic tubes do not allow of normal passage. A hypoplastic uterus is incapable of normal semen reception and fixation of the embryo. The secretions of a hypoplastic uterus are abnormal and thus often hostile to sperm. The non-development of the cervix, pinhole os, in the hypoplastic uterus make for defective passage of the semen into the uterus.

Ovarian tumours and infections. Displacements of the uterus. Prolapse is significant in sterility only if the cervix descends too low for insemination. Anteflexion, to which so much importance was attributed until a short time ago, is now recognised as a normal status, within wide limits. Acute anteflexion, however, may cause sterility, because if the cervix is tilted too far forward the reception of semen is faulty. Further, intense anteflexion occurs in utero-ovarian hypoplasia, and is thus not the cause of sterility in these cases but a concomitant of the ovarian hypoplasia, the real cause of sterility. It is an associated and not a causal manifestation. Retroflexion, again, is not in itself a cause of sterility according to Meaker and other gynæcologists, except when it leads to intense anteversion of the cervix and thus to faulty reception. Insemination is usually impossible when the os externum is covered by the anterior vaginal wall. Further, uterine retroflexion may be associated with prolapse of the ovaries and congestion of these organs interfering with ovogenesis.

Infections of the uterus. Endometritis interferes with the nidation of the ovum.

Cervical infections can effect alterations in the cervical mucus, but their role is perhaps exaggerated. Women with gonorrhœal endocervicitis often conceive. Huehner found that in mixtures of semen and fresh gonorrhœal pus the vigour of the spermatozoa remained unimpaired.

Fibroma. The role of uterine fibromyoma in sterility is much discussed. A relationship undoubtedly exists between them, as many women who have fibromyomas are infertile, but fibromyoma is not the cause of the sterility. It is more probably, as some authors hold, a manifestation of the infertile organism. Fibroids arise in default of the normal function of the uterus, namely, pregnancy. At all events there can be no doubt that certain fibromas constitute an impediment to pregnancy. Cornual myomas, even small, are factors of infertility because they obstruct the interstitial portion of the Fallopian tube. Submucous fibroids of any size interfere with nidation. All fibromyomas in women of childbearing age must be treated by myomectomy.

Pelvic inflammations. These may disturb ovogenesis by interfering with ovarian function, and by obstructing the tubes with adhesions. Gonorrhœa in particular leaves the tubes functionally worthless. Tuberculous salpingitis also is important. Puerperal and post-abortion infections, especially the latter, play a sinister role. Infections of other types also may account for a proportion of tubal occlusions.

Chronic passive congestion of the pelvis. Meaker regards this as a very common pathological state of the female pelvis. It involves the ovaries and disturbs ovogenesis. It involves also the tubes, causing œdema and mucous plugs within the lumen and thus interfering with potency. This congestion may be the result of a retro-displacement of the uterus, of liver disease, or of more systemic factors.

Vaginismus. This is usually psychic in origin, and interferes with the vagino-uterine reception factor.

Defective coitus. Important features are premature ejaculation by the male, which makes for defective insemination of the uterus, infrequent intercourse, particularly during the fertile period of the cycle (9th to 18th days after the beginning of menstruation). The methods of contraception, if any, also should be investigated.

Constitutional Investigation of the Infertile Woman.

The following factors have to be considered by the endocrinologist.

Hereditary factors. These must be thoroughly investigated, as they give a definite guide to prognosis.

Psychological factors. From a general point of view sterility is a complicated functional disturbance in which somatic as well as psychic factors participate. By some unknown mechanism psychic factors undoubtedly play a part in conception. Psychological hostility is probably more important than hostility of cervical secretions in infertility. Further, psychogenic factors predominate in the genesis of many endocrine disturbances and constitutional inadequacies which disturb the mechanism of infertility.

Wittkower has attempted to study the personality of sterile women. He found that the majority of these patients were diffident in manner and juvenile, or younger than their years, in appearance. They had often been the youngest or the only child, over-attached to the family rather than to either parent, intensely shy, disliking school, as adults interested in their personal appearance

to an unusual degree, imbued by an obvious desire to attract. Neither before nor after marriage had they experienced any genuine adult sexual feeling. They were frigid and incapable of any deep affection. Most infertile women I have seen did not show at all the features described by Wittkower, and I do not think that the personality of the sterile woman belongs to a special type. Various personality types are encountered according to the basic endocrine-metabolic disturbances leading to sterility. The endocrinologist has to individualise and determine the psychological conflicts and disturbances. of his particular patient.

Frigidity is an important factor in most cases, although frigid women are not necessarily sterile.

Factors of malnutrition. Malnutrition causes endocrine disturbances and constitutional inadequacies which disturb the mechanism of fertility. More specially they disturb the ovoproductive factor. Papanicolaou showed long ago the fragility of the Graafian follicle. Loeb has shown that underfeeding in female guinea-pigs prevents maturation and causes atrophy before the follicles reach a medium size. Protein starvation needs particular consideration because it entails cellular malnutrition, and the sex cells are the first to suffer. Tryptophane deficiency has recently been well demonstrated as a cause of infertility. Vitamin and mineral deprivation also are important. The role of vitamin E as a synergist of the progestin system and thus as a regulator of the uterine nidation factor is well known.

Factors of hygiene, exercise. The importance of these factors can easily be understood in view of the fragility of the Graafian follicle. Breeders have often observed that when cows are under-exercised they show heat less often and ultimately become infertile. I have noted that couples of sedentary habits have achieved a child after a good season of winter sports although numerous hormonal injections had been ineffective.

Chronic intoxications. These depress ovogenesis directly and contribute to the establishment of endocrine diseases and various metabolic disturbances. Although they have been incriminated experimentally more than clinically, alcohol, lead and morphia intoxications should be considered.

Chronic infections. Malaria and syphilis enter chiefly into consideration.

Hepatic disturbances. I have often seen infertility in women with hepatic disturbances, and not only among those with gross lesions. The liver is the great metabolic organ. Even slight disturbances upset the body chemistry, reacting on the fragile Graafian follicle.

Endocrinopathies. The importance of hormones in the mechanism of reproduction makes the role of endocrinopathies obvious. Meaker writes that 57 per cent. of his infertile patients, male and female together, show evidence of endocrine disturbance. Rowe, after studying 4,000 patients, wrote: "The endocrine patients were definitely less fertile than those with non-endocrine disease, even though the latter group contained an appreciable number of syphilitics and patients with other conditions recognised as influencing fertility." If we consider the formes frustes the role of endocrinopathies assumes

even more importance. Endocrinological examination is the crux of the constitutional investigation of the sterile woman. Any endocrine disturbance may be a factor of sterility, and thus all endocrine systems must be explored by clinical and biochemical methods. The basal metabolism and the carbohydrate, calcium and protein metabolisms are all important. Obese women are often sterile because they have endocrine disturbances.

Menstrual disturbances are prominent in the endocrinopathies leading to sterility. 30–70 per cent. of women with infrequent and scanty periods are absolutely sterile. The converse, however, is not the case. Regular menstruation is not always a sign of fertility, and it should be remembered that many women menstruate without ovulation, *i.e.,* they bleed from a secretory and not a progestational endometrium.

The habitus must be studied, as it is a manifestation of endocrine and genetic function. In spite of the work of Berkow, however, particular morphological types do not seem to be associated with sterility. The problem is wider, sterility being associated with particular endocrine and genetic disturbances.

Constitutional inadequacies. This is a physiopathologically vague term, but well understood clinically. It is true that physiopathologically some metabolic disturbances depend on genetic (hereditary), psychological, nutritive and endocrine factors. Many of them are the "anæmias" of our fathers. Meaker writes: "Stock-breeders and veterinarians have long recognised the influence that states of depression exert on the fertility of animals; likewise laboratory workers have found it easily possible to depress fertility by inducing various types of general debility. But only in recent years have physicians taken account of this important fact . . . The total number of cases in which the elimination of a constitutional depression has resulted in the clinical relief of sterility is now sufficiently large to rule out any likelihood of pure coincidence."

Neuro-vegetative conditions. The neuro-visceral system plays an important part in reproduction, and abnormal reaction of the sympathetic or parasympathetic systems should be investigated. Uterine and tubal movement, and probably ovulation, are in part at least under neuro-visceral control.

Constitutional Treatment of the Infertile Woman.

The physiopathology and the investigation of female infertility show constitutional factors to be more important than the purely gynæcological factors. As long ago as 1928 Novak wrote: "It is possible that our helplessness in this great problem is the outcome of too much attention to anatomical defects and too little to a possibly perverted physiology."

However, simple delineation of the physiopathology of infertility shows the difficulties of the application of physiological principles. There are so many gaps and so many hypotheses in the mechanism of reproduction. Even the clearly known points, such as the physiology of hormonic control, are not applied easily, because the problem is one of hormonal balance, not deficiency

of any particular hormone. Thus the question of dosage becomes very delicate and in fact cannot have a physiological basis.

The position, however, is not hopeless. On a small scale it is similar to that which confronted Kant when, with the critique based on his " Theoretical Reason," he reached absolute scepticism and negation, but found a more solid basis for the understanding of life when he applied his " Practical Reason." We also have a practical reason, the clinical experience and clinical diagnostic skill based on clinical intuition. Clinical practice has often successfully outrun physiological research.

Good results from constitutional treatment of the sterile woman can be achieved by means of careful constitutional investigation and the application of constitutional methods, centred mainly on endocrinotherapy on the basis of this investigation, and with the help of the clinical empirical method. By a careful following up, by detecting the slightest changes and reactions with a keen clinical eye, much can be done notwithstanding the incomplete physiological knowledge.

This constitutional treatment cannot be described as it is essentially individual, but something can be said as regards endocrinotherapy. Results have been obtained by various hormones, the choice depending on determination of the individual reactions. Œstrin has been beneficial, particularly in cases of uterine hypoplasia. Some authors use strong doses, others a smaller quantity. *A*-gonadotropin (F.S.H.) also has given very good results (David and Koff). Thyroid is frequently indicated. These three hormones are used in alternation in most cases. Chorionic gonadotropin is useless and probably noxious.

Röntgen treatment of the pituitary has been advocated recently but further study is necessary, as pituitary irradiation may overstep the mark.

As regards other constitutional measures, it is important to remember the advice of Knaus and when sending these patients to watering places to have them accompanied by their husbands.

CHAPTER XXXI

ENDOCRINE METABOLIC FACTORS IN MALE INFERTILITY

Physiopathology. Male fertility depends on the normal functioning of various factors: (*a*) the formation of spermatozoa; (*b*) the maturation of spermatozoa; (*c*) the passage of spermatozoa through the genital tract; (*d*) the ejaculation of spermatozoa within the vagina. These factors, their nervous, endocrine and nutritive control and the possibility of their disturbance, are investigated first.

I. Formation of spermatozoa. The first phase in the formation of spermatozoa is transformation of spermatogonia into primary spermatocytes, which possess 24 chromosomes apiece including the XY pair. This phase is not under hormonal control.

The second phase is the reduction-division phase. The primary spermatocytes are divided, each giving rise to two secondary spermatocytes. Each secondary spermatocyte possesses half the chromosomes of the primary, thus 12 chromosomes. Amongst them, as the XY pair has been divided, each secondary spermatocyte possesses either the X or the Y chromosome. This phase is controlled by pituitary gonadotropins, probably mostly by the *a*-gonadotropin.

The third phase is transformation of the secondary spermatocytes, first into spermatids and then into spermatozoa. This phase is under the control of testosterone, at all events in part.

Spermatozoa appear in man about the 12th–15th years and are produced the whole year round, in contrast to certain animals which produce spermatozoa only at certain seasons corresponding to breeding time, period of rut.

The hormonal control of spermatogenesis is demonstrated by cessation of that process after removal of the important hormonal centre, the hypophysis. The injection of testis extracts, chemical androgens and even progesterone can prevent stoppage of spermatogenesis in such an event, but only if given immediately, *i.e.*, before damage by hypophysectomy has been accomplished.

Spermatogenesis is also under nutritive control. Yeast extract also prevents retrogression of spermatogenesis after hypophysectomy. In *B*-complex deficiency spermatogenesis is impaired, as both clinical and experimental work have shown (Biskind). Vitamin E also exerts a regulatory function, as shown by disturbance of spermatogenesis in E-vitamin-deficient animals. In human clinic, however, the role of vitamin E has not been demonstrated. Holt has shown that spermatogenesis is disturbed by deficiency of certain aminoacids, mainly arginin.

Certain physical factors also control spermatogenesis. The stimulating effect of light has been shown in birds. A certain optimum temperature is needed, and for this reason spermatogenesis is impaired in cryptorchidism and febrile states inhibit it temporarily.

II. Storage and maturation of spermatozoa. The testis consists essentially of many hundreds of small tubules (seminiferous tubules) each about 1–2 feet long and about as large in diameter as a thread of sewing silk (Corner). They are arranged in loops, all opening into a network of channels at the hilum of the testis, whence they are drained off by a dozen larger channels into the epididymis. In these tubules the sperm cells are formed. They first cling to the cells that line the walls of the tubules, then drop off and are carried towards the epididymis. At that stage the sperm cells are immature and non-motile, and if discharged in that state they could not fulfil their task and reach the egg cell. They require a further period of ripening and conditioning until they become fully motile and potent. Furthermore, the seminal fluid in which they are to be carried must be formed and added to them.

Thus from the dozen larger channels that drain the seminiferous tubes the spermatozoa pass into a single tube about 21 feet long tightly coiled into a

dense mass, the epididymis. This is lined with secretory cells whose function is to secrete substances for the nutrition and maturation of sperm cells. These take many days to be carried along the whole length of the epididymis, and during this journey they have the time to mature. Their passage is also a phase of storage during which they mature and become motile. An optimum of *p*H is necessary for semen, and has been fixed at a little over 7, *i.e.*, with a slight tendency to alkalinity.

III. Duct phase. Passage and seminal fluid maturation. The spermatozoa and the seminal fluid which surrounds them pass into the duct system, principally during ejaculation, and there the seminal fluid is completed for spermatozoal function and metabolism. The duct system is constituted by the vas deferens (one on each side). The two ducts unite below the bladder and enter the urethra just after it makes its exit from the urinary bladder. The combined seminal and urinary channel enters the prostate and passes into the penis. Before uniting, each duct gives rise to a small saccular offshoot, the seminal vesicle. The seminal vesicles, each 4 inches long but folded to half the length to lie in place, are not reservoirs of spermatozoa but glands of external secretion that produce a clear gelatinous substance which becomes part of the seminal fluid. In the prostatic section of the genital duct the sperm receives the prostatic secretion, which completes the constitution of the spermatic fluid. All formations contributing to the completion of the seminal fluid are under neuro-hormonal influence, mainly that of the β-gonadotropin-testosterone system, and probably under neuro-visceral (neuro-vegetative) influence.

Urological Investigation of the Infertile Man.

In the same manner as female sterility needs a joint effort by endocrinologist and gynæcologist, male sterility is the joint province of endocrinologist and urologist. The following is a general outline of the urological data necessary.

The most important element is an investigation of spermatogenesis, of which only a general plan is given here. The simplest procedure is examination of the ejaculated semen. There is a norm for number, morphology, motility and endurance. If this norm is satisfied there is evidence but not absolute certainty of fertility.

Sperm counts in normal cases range from 75–200 millions. Most highly fertile men have counts over 100 millions. In pathological cases all degrees of reduction down to complete azoospermia are encountered. It is often held that figures below 50 millions mean infertility, but Hotchkiss has remarked that fertility has occurred with as low a count as $2\frac{1}{2}$ millions.

Abnormal forms occur normally under 15 per cent. In individuals of doubtful fertility 40 per cent. and even higher figures are seen.

Non-motile forms range in normal men from 10–15 per cent. A higher percentage indicates a disturbance of spermatogenesis. Spermatozoa from average fertile men remain active for 12–24 hours at room temperature. Abnormal specimens lose their motility in 8 hours or less.

More complicated methods of investigation, often necessary, are epididymal aspiration and testicular biopsy.

The urological investigation proceeds next to search for:

Orchitis and cryptorchidism.

Large varicoceles. These may impair spermatogenesis by interfering with the circulation of the testis.

Bilateral hernia. This results frequently in impaired testicular circulation and function.

Narrowing of the ejaculatory ducts, and narrowing at any part of the seminal tract. A most common site of obstruction is the lower pole of the epididymis. Chronic gonorrhœa plays a great role in these conditions.

Constitutional Investigation of the Infertile Man.

The constitutional investigation of male infertility, the work of the endocrinologist or constitutionalist, bears on the following points.

1. Hereditary genetic investigation.

2. Investigation of nutritive factors. Defective nutrition impairs spermatogenesis, particularly vitamins B and E deficiency. The condition of the digestive organs enters into this investigation.

3. Investigation of general hygienic conditions. All faulty habits—lack of exercise, lack of fresh air, bad working conditions—impair spermatogenesis. Experimentally, animals in confinement lose spermatogenic function, although they may finally adapt themselves to their new environment.

4. Investigation of psychogenic factors. Emotions, and particularly mental conflicts, impair the neuro-endocrine control of spermatogenesis, which itself probably develops through the vegetative nervous system.

5. Investigation for previous debilitating illnesses and existent infective conditions. Factors important in male infertility are mumps with orchitis, scarlet fever, recurrent tonsillitis, anæmia, gonorrhœa, malaria. Febrile conditions cause a temporary loss of spermatogenesis.

6. Investigation for intoxications. Alcoholism, lead poisoning and morphia intoxication are the most important toxic factors of male infertility. They act either directly on the seminiferous tubules or disturb the various phases of male reproductive physiology by determining neuro-endocrine disturbance.

7. Investigation of the constitutional balance, *i.e.*, the mode of function of psyche, nervous vegetative system and neuro-metabolic system. This last is the most important factor, and includes principally the protein, carbohydrate, water and electrolyte metabolisms, and the diagnosis of endocrinopathies.

8. Investigation of the condition of all organs, since organic lesions, by upsetting the general metabolism, react on fertility.

Constitutional Treatment of the Infertile Man.

The principles of constitutional treatment, as previously described for female infertility, must be applied. On the basis of a complete constitutional

investigation suitable psychotherapeutic, dietotherapeutic, physical and pharmaceutical procedures are employed.

Endocrinotherapy plays the preponderant role. Various hormones have been used, according to the indications. *A*-gonadotropin is given in the form of equine gonadotropin, *β*-gonadotropin in that of chorionic gonadotropin from pregnancy urine. Results vary. At all events gonadotropins should be used in small doses, but need careful sperm counts besides general constitutional supervision, because in some cases they seem to increase the abnormal forms of spermatozoa. Testosterone restores spermatogenesis when applied in small doses, according to Laqueur, a view confirmed by Rubinstein and Kurland. Others, however, have obtained negative results. In strong doses, testosterone depresses spermatogenesis. The gonadotropin and testosterone treatment of male infertility is undoubtedly active, but the technique of application is very delicate. On the whole after a first flush of enthusiasm it seems that the actual technique of sexual hormone therapy gives poor results.

Thyroid has given the best results, particularly in individuals with low basal metabolism. The cases in which this treatment has been successful were not cases of real myxœdema but formes frustes manifested chiefly by the biochemical signs of hypothyroidism.

B-complex vitamin has succeeded in cases where diet was inadequate and in which headache, irritability, fatigability and lumbar ache were noted, as also in cases with glossitis, stomatitis and skin lesions. Vitamin E has given less definite results.

CHAPTER XXXII

ADRENAL AND GONADAL PUBERTAS PRÆCOX

Adrenal Male Pubertas Præcox.

The most distinct cases are those connected with an adrenocortical carcinoma. They are very rare. Others are linked with a genetic hyperplasia of the adrenal cortex. Both these forms represent a primary adrenal hypercortinic genitalism beginning after birth but very early in life.

It is not known whether a cerebro-pituitary hypercorticogenitalism can give rise to male adrenal pubertas præcox. It is possible that the pubertas præcox which follows encephalitis and that connected with a tumour pressing on the hypothalamus belong to this class. It is possible also that many formes frustes of pubertas præcox may be due to cerebro-pituitary hypercorticogenitalism.

The Complete Form. The general history is one of accelerated development of stature, muscularity and sexual characters with obesity, but usually without a corresponding acceleration in mental development.

The growth and genital development may show acceleration at any age. The youngest case on record is that of Fraser, in which the penis began to

enlarge at the age of six months and the one-year-old boy showed a bone age of five years and a penis and prostate (but not testicles) of eighteen years. An adrenocortical tumour was found at operation.

When these boys are seen for the first time they immediately give the impression of being bigger than their age. Tallness, intense muscularity and obesity are characteristic. Tallness is nearly constant but only up to a certain stage. Growth stops when the epiphyses close (androgenic effect), and as this closure occurs earlier than normal these boys appear small for their age later in life. The earlier macrosomic aspect is followed by a microsomic appearance. The intense muscularity, an exaggeration of a male sexual character, is often so striking that the term " infant Hercules " is used. These boys do the manual work of an adult and associate with adults in various callings. Obesity is sometimes gross, and pushes the muscularity into the background. It is not the plumpness of the child but the plethoric obesity of the adult. The cheeks swell with fat, and in addition to the general obesity there may be local rolls or pads of fat on neck, breasts and back. The plethoric condition of the cutaneous vessels gives the characteristic facies of the " burly brewer's drayman in miniature." Radiology shows an advanced bone age.

The sexual syndrome is the next striking feature. Here also accelerated development of the sexual organs and functions far beyond the age is noted. At five or six years of age pubic and axillary hair, penis, scrotum and testes are well developed. Erections and seminal ejaculations occur. The sex age far exceeds the calendar age.

The intellect, however, lags behind the accelerated physical development. It usually corresponds to the calendar age and is sometimes even retarded.

The urine shows an excess of androgens and œstrogens.

In neoplastic cases an adrenal tumour may be detected clinically, but more frequently by radiology after insufflation of the adrenals.

The course of the disease in neoplastic cases is that of the causal tumour, which is of low malignancy.

Formes Frustes. Formes frustes of pubertas præcox are frequently seen in the practice of an internist interested in constitutional disorders. Undoubtedly many of them belong to the adrenal group and result from a cerebro-pituitary hypercorticogenitalism usually determined by a genetic lability of the adrenocortin system.

Boys with formes frustes are relatively short and stocky. The initial macrosomia of the complete form is too transitory and unimportant to leave its mark. There is no obesity but muscular development is very high. The teeth are remarkably good. Such patients are microskelic, their span being smaller than the height and the lower segment relatively smaller than the upper (in reference to the special infantile proportions). This is due to early closure of the epiphyses. The skin is often thick. Acne and hypertrichosis of the lower part of the body are noted.

The psychological characteristics are interesting and often dominate the

Fig. 9
MIDDLE, ADRENAL PUBERTUS PRÆ COX MALE AGED SIX. *RIGHT*, NORMAL CHILD SAME AGE. *LEFT*, CHILD AGED THIRTEEN

clinical picture. In spite of their muscular development such boys are not always physically active, and may prefer indoor amusements and occupations to sports. Abnormal sex behaviour, hetero- or homosexual, is seen in many cases. Abnormalities of general behaviour—incorrigibility, truancy and larceny—are relatively frequent. Cerebration is usually below normal.

Hypertestosteronic Male Pubertas Præcox.

In its typical form this is determined by an interstitial tumour of the testis, and is therefore physiopathologically a testicular hypertestosteronism. Some milder cases are probably the result of cerebro-pituitary hypertestosteronism, the hypersthenic reaction of the testosterone system beginning at its diencephalic centre. It is possible also that some cerebral neoplastic and encephalitic cases occur through a cerebro-pituitary hypertestosteronic mechanism.

The clinical picture of testicular neoplastic pubertas præcox is that of the complete form of male adrenal pubertas præcox except for a testicular instead of an adrenal tumour. The first case described was that of Sacchi in 1895. Cases have been reported by Parkes Weber and others. Treatment consists in removal of the tumour.

Cerebro-pituitary hypertestosteronic male pubertas præcox is usually manifested as formes frustes similar clinically to those of adrenal male pubertas præcox already described.

Cerebro-Neurovegetative Male Pubertas Praecox. Male pubertas præcox has been described as connected with a diencephalic tumour or an encephalitis. Such diencephalic disturbances can act through the mechanism of a cerebro-pituitary hypercorticogenitalism or a cerebro-pituitary hypertestosteronism, and these cases may therefore be special etiological forms of adrenal or hypertestosteronic male pubertas præcox. They may act also, however, by modifying the reactivity of the cells of the sexual formations *via* a direct nervous vegetative route, and these cases can be described as cerebro-neuro-vegetative male pubertas præcox.

In the case of Le Marquand and Russell the causal tumour was small and attached to the right corpus mamillare and tuber cinereum. In the case of Heuyer and associates, the causal tumour was an ependymoglioma of the hypothalamus that had destroyed the mammillary bodies and the tuber cinereum. In Vicker and Tidswell's case the causal tumour was an astrocytoma, which also had destroyed the mammillary bodies and the tuber cinereum. Cases following encephalitis have been described by Ford and Guild and by Stern.

The few cases of pubertas præcox due to diencephalic tumours or post-encephalitic conditions show the picture described for adrenal male pubertas præcox. The only differential symptoms are manifestations of intracranial hypertension and certain hypothalamic manifestations such as somnolence and diabetes insipidus.

Adrenal Female Pubertas Præcox.

This is the female counterpart of adrenal male pubertas præcox. It is not a purely female pubertas præcox but includes some virilisation. The first case of female pubertas præcox connected with the adrenals was described in 1756 by William Cook, but the disease was established distinctly in nosography by Bulloch and Sequeira in 1905.

This condition results also from a hypercorticogenitalism beginning very soon after birth, at all events in infancy. This endocrinism may be local adrenal and determined by an adrenocortical carcinoma similar to that described for virilism, a genetic hyperplasia of the adrenal cortex. It may be cerebro-pituitary, in which case adrenocortical hyperfunction and hyperplasia may be due to the intense adrenotropic drive. In cerebro-pituitary female pubertas præcox a genogenic abnormality of the corticogenitalin system is an important factor. Various factors, possibly including encephalitic processes, act on the hypothalamic centre of the labile cortigenitalin system, and the disease is manifested.

Clinic. The disease is characterised by acceleration of development of growth and sexual characters, and in many cases by obesity and general masculinisation of the girl. It is a pubertas præcox with masculinisation. The child races through the stages between birth and puberty, simultaneously acquiring male features.

Morphologically an initial spurt in growth makes these girls very tall for their calendar age. Later, however, the premature closing of the epiphyses stops growth and nanosomia takes the place of macrosomia.

Muscular development is striking. The muscles develop not only early but intensively into those of a male. Hair is abundant and assumes the male distribution of scalp hypotrichosis, body hypertrichosis and triangular pubescence. It develops early in life. Small girls have abundant pubic and axillary hair, and even moustache and beard. The skin is thick, often riddled with acne (the acne of male puberty). The general impression is masculine.

The obesity is confined to the upper trunk, thus representing an exaggeration of male fat distribution. It is the plethoric obesity of the adult, not childish chubbiness. In mild cases it gives the girl the appearance of premature matronliness. The bone age is advanced.

The sexual syndrome also is one of intensely accelerated development with masculinisation. The hypertrophy of the clitoris is essentially characteristic. At the age of three or five or even in the first year of life the clitoris enlarges and pubic hair appears. Menstruation may occur very early (at three years and nine months in Riche's case) but is usually scanty and ceases early. Some girls with adrenal pubertas præcox never menstruate. Mammæ are not developed. All this contrasts with ovarian pubertas præcox and its early, abundant and persistent menstruation, as adrenal pubertas præcox is under the influence of the corticogenital hormone which is masculinising and therefore inhibits menstruation.

Mentally these girls correspond to their calendar age. Older girls with this disease manifest certain psychological disturbances due to their physical abnormality. They prefer to play with boys, not as an element of libido but because they feel more akin to them in general temperament and pastimes. Detailed psychological studies are lacking.

The organic systems offer no particular feature, but hyperpiesia has been noted, especially in van der Bogert's case of a two-year-old girl with 180 systolic and 110 diastolic. Biochemically 17-ketosteroids are increased in the urine, particularly in neoplastic cases. Broster finds " free male hormone " in his cases.

The course of neoplastic cases is directed by the neoplasm, which is of low malignancy. The condition may be maintained for some years but ultimately the patient dies from cachexia due to metastases or from Addison's disease resulting from destruction of the adrenocortical tissue by pressure of the tumour. Operated cases fare better and symptoms retrocede, but relapses occur.

Cerebro-pituitary cases, apart from the exceptional cerebral neoplastic cases, show a milder course. Some of them may continue and the precocious puberty with virilism merges into adult virilism. A few cerebro-pituitary mild cases improve with œstrogenic hormones, but in accentuated conditions adrenalectomy is the method of choice. The technique has been studied and described by L. C. Broster and his collaborators, to whose works the reader is referred for more details.

Hyperœstrinic or Ovarian Female Pubertas Præcox.

This is the female counterpart of hypertestosteronic male pubertas præcox. It is due to hyperœstrinism occurring early in infancy and due to a granulosa tumour of the ovary. Such tumours vary in size from small microscopic nodules to growths of 15–20 cm. in diameter. They are unilateral with few exceptions. They are composed mainly of granulosa cells and have a low degree of malignancy. A cerebro-pituitary hyperœstrinism occurring before puberty can also be accepted as the physiopathological basis of many formes frustes of ovarian female pubertas præcox. The latter are described as " constitutional." In fact, they are determined by a genogenic lability of the œstrin system.

The Primary Ovarian or Neoplastic Form. Clinically this is a purely feminine pubertas præcox. As in adrenal pubertas præcox, there occurs an initial spurt in growth followed by arrest of growth from premature union of the epiphyses. The whole appearance is distinctly feminine, and the breasts in particular are well developed. Obesity is not marked, neither is muscularity. Acne does not develop. Hair is abundant on the head, pubic and axillary hair appear early, there is no body hair and the pubescence is of female type. Altogether the impression is that of a girl of fifteen or sixteen when the patient is of any age between nine and twelve.

Menstruation starts very early, even in the second year of life. It is abundant and continues regularly. The external genitals are well developed

but the clitoris is not hypertrophic. The breasts are so well developed that they resemble those of a post-puberal girl. It is not known whether pregnancy is possible in such cases.

Œstrogens are increased in the urine. The constant finding of 15 or more rat units of active œstrogen in the 24-hour urine (the quantities current in normal adult females) points to a granulosa tumour. Signs of ovarian tumour exist, and the abdomen may even bulge if the tumour is large.

The course of the disease is that of the tumour, which is not highly malignant. Treatment is purely surgical.

The Cerebro-pituitary Forms. These are often described as "constitutional." In fact they arise from a combination of genogenic lability of the hypothalamus-alphagonadotropin-œstrin system with a genetic hyperreactivity of the cells of the body to œstrin. In most cases they are formes frustes and often run in families.

An exaggerated form of this essential female pubertas præcox is presented by those young girls who become pregnant. Here a special genetic disturbance makes possible the maturation of Graafian follicles and consequent production of ova before the normal puberal stage. The reactivity of the ovaries probably changes and renders them sensitive to pituitary gonadotropins prematurely.

Professor Edmundo Escomel, of Lima, reported in 1939 pregnancy in a child five years of age. The girl had started menstruation at eight months, and at four years the breasts were developed and pubic hair had appeared. The girl was delivered at term, at the age of $5\frac{3}{4}$, of a healthy infant weighing 2,700 grams and the mother left the clinic in perfect health. This is the earliest case of pregnancy on record. It cannot be considered as an ovarian pubertas præcox because the ovaries showed no abnormality. Nor can it be attributed to an adrenal pubertas præcox, because adrenal factors are defeminising. A case of pregnancy at the age of eight was reported by Molitor in 1878, and J. D. Rolleston cites a case of A. Restrefio in which pregnancy occurred at the age of seven.

Neurovegetative Female Pubertas Præcox.

Cases of female pubertas præcox following the lines of the hyperœstrinic form have been described as resulting from tumours of the hypothalamus and encephalitic conditions. It is not known whether these act through the mechanism of a cerebro-pituitary hyperœstrinism or by a purely neurovegetative influence of the sexual formations. Gesell and his associates have described the case of a Jewish girl who showed physical signs of pubescence in the first year of life and menstruated at the age of three years seven months. At the age of eight she was found to have a cerebellar astrocytoma. In Cappell and Dott's case the causal tumour was found in the floor of the third ventricle in the region of the mammillary bodies. In Dorf and Schapiro's case a chronic hydrocephalus was considered the only possible cause for a female pubertas præcox. Ford and Guild have described cases of the disease following encephalitis.

DIAGNOSIS

The syndrome of pubertas præcox is easily diagnosed. The adrenal, gonadal and neuro-vegetative forms have to be differentiated. Pineal pubertas præcox should be differentiated from adrenal and gonadal male pubertas præcox (see appropriate chapter).

CHAPTER XXXIII

HYPOTESTOSTERONIC FEMINISM
(HYPOTESTOSTERONIC MORPHO-PSYCHOLOGICAL ANDROGYNOIDISM)

Feminism is a morpho-psychological androgynoidism, in other words a male intersexual condition in which intersexualisation, viz., feminisation, bears on the morphological and psychological sexual characters. In hypotestosteronic feminism the basic physiopathological disturbance is hypotestosteronism occurring after birth. It is thus akin to acquired hypotestosteronic eunuchoidism, and it is in fact acquired hypotestosteronic eunuchoidism with predominance of feminisation due to unchecked action of male œstrin.

The etiology and physiopathology is that of hypotestosteronism in general, as described in male eunuchoidism and adiposogenital dystrophy.

The Common Form. Such patients show the habitus of eunuchoidism, with its macroskelic thinness, or of adiposogenital dystrophy. The predominant feature, however, is the feminine appearance, the broad hips, the swinging gait, and often the fully developed breasts. Mentality is feminine. Libido also, in some cases, is of female type, and thus passive male homosexuality is encountered. The general symptomatology is that described in the appropriate chapters of male eunuchoidism and adiposogenital dystrophy.

The Psychological Forms. Special psychological forms are frequent. The most important are the dilettante form, the transvestist form and the homosexual form. They are characterised by predominance of feminisation in the psychological features.

The dilettante form is more a biotype than a real constitutional disease. Such individuals lack the typical male psychology of will to power, mastery of emotion, action directed outwards and work with a direct object, but show the opposite features. Balzac, that great psychologist, used to term *eunuques de l'art* those poets and writers always surrounded by a court of admirers and productive of nothing but talk for the sake of talking. There was in the *causeur* of the old French salons an element of intersexuality. In point of fact the physician skilled in morphology can detect in such persons female morphological features. The muscular relief is not distinct. Fat often appears around the pelvis. The skin is white and delicate. The body and face show very little hair, while the scalp hair is very abundant. Possibly the long hair cultivated by certain artists has an intersexual meaning, although in many cases it is nothing but imitation and pose. Sexually these individuals are

not markedly potent as males, although they talk volubly about sex. In some of them there is a tendency, usually Platonic, to homosexuality. Donjuanism is a variety of this form. The general view is that Don Juans have an excess of virility, but I think that the fine psychological acumen of the Spanish endocrinologist Maranon is right. Don Juans show in effect the emotional sexual instability and restless search after emotion that are more female than male features.

The transvestist form finely described by Magnus Hirschfeld is characterised by the presence in males of the female love of adornment, reaching the desire of dressing as women. The notorious eighteenth-century adventurer, the Chevalier d'Eon, is a brilliant historical example. The term " Eonism " is applied by Havelock Ellis to male transvestism.

Hypotestosteronic male homosexuality represents the highest degree of this psychological intersexualisation of endocrine origin. The intersexual nature of male homosexuality was first pointed out by the jurist Ulrich, himself a homosexual, who in 1862 defined such individuals as " anima mulieris in corpore virile inclusa." It was Krafft-Ebing, however, who demonstrated conclusively the intersexual nature of male homosexuals, showing the existence of other feminine traits in such persons. The male homosexuality which represents a psychological form of feminism is in typical cases a passive homosexuality. According to Wright such homosexuals show a preponderance of œstrin in their urine. Morphologically and psychologically they exhibit many feminine features. Only hypotestosteronic homosexuals are liable to be improved by testosterone treatment.

Only a fraction of male homosexuals are hypotestosteronic in nature. Male homosexuality is a complex process. The homosexuality of the ancient Greeks was unrelated to intersexuality but originated in certain social and educational conditions tainted by a particular æsthetics. It was in fact their " fagging " system. Other cases of male homosexuality are due to excessive virility demanding satisfaction by various means and to communal life among men precluding satisfaction of the sexual instinct with women. Other cases represent an intersexual condition of deep constitutional or genetic nature. Only a few male homosexuals are hypotestosteronic intersexuals. Most individual cases of male homosexuality are mixed, and in all of them educational and social conditions intervene. This nosographical classification is thus artificial but is of help in understanding the individual patient.

All cases of hypotestosteronic feminism require treatment on the lines indicated for eunuchoidism, but treatment centres especially on testosterone and psychotherapy.

Differential Diagnosis

Deep Constitutional Feminism. In this form the genetic regulators of masculinisation are disturbed. The balance between masculinising and feminising genes is broken. The masculinising genes lack sufficient strength to stimulate the male potentialities and inhibit the female potentialities of the field, and thus insufficient masculinisation occurs.

Individuals with this form of intersexuality are men whose general aspect is feminine, but not to the point of caricature presented by certain eunuchoids or adiposogenital dystrophics. They are harmoniously and æsthetically beautiful. These men have normal feminine, not eunuchoid, proportions. The development of the genital organs is normal but male libido is weak or of female type and thus passive homosexuality is practised. The psychology is essentially feminine. Although in these subjects sex reversal occurs at the genetic organiser phase and the condition is thus deep constitutional, environmental factors of social milieu, education and pampering of these beautiful girl-boys accentuate the mental feminine traits and promote the homosexual component.

Deep constitutional feminism can manifest itself as any of the psychological formes described for deep hypotestosteronic feminism. Thus many male transvestists, and particularly many male homosexuals, are of deep constitutional and not of endocrine origin.

CHAPTER XXXIV

ADRENAL AND GONADAL VIRILISMS

Virilism is the first degree of intersexualisation of a female (virilisation), thus the female counterpart of feminism. It is a morpho-psychological gynandroidism. It is characterised by masculinisation of the morphological and mental features and defeminisation of female organs and functions. According to the constitution regulators predominantly involved in these conditions, various forms can be described.

Adrenal Virilism.

Physiopathology. This, probably the most frequent variety of virilism, is determined by a hypercorticogenitalism occurring after puberty. The corticogenital system may be involved in its glandular centre (primary adrenal virilism) or in the diencephalic centre of the system (cerebro-pituitary adrenal virilism). In all these forms the adrenocortical sexual hyperfunction occurs after puberty, for when it starts before birth it gives rise to female genital hermaphroditism and when it occurs in infancy the result is a female pubertas præcox.

Primary or glandular adrenal virilism is a neoplastic adrenal virilism. It is due to a hypersecreting adrenocortical tumour, usually an adrenocarcinoma, exceptionally, as in the case of Gordon Holmes, an adenoma. This tumour acts by secreting excessive cortigenitalin, or more precisely an excess of the sexual factors of adrenocortical incretion. The condition is thus an adrenal hypercorticogenitalism. It is not necessary to postulate an abnormal secretion from such tumours.

Adrenocortical adenocarcinomas are usually unilateral. Their proportions vary. They may be as small as a nut, but may reach the 1,990 grams of weight

recorded by McGavack. Not all adrenocortical adenocarcinomas are endocrine, many showing a purely tumoral symptomatology. Microscopically these tumours are composed of atypical cells resembling partly those of a carcinoma and partly those of a sarcoma.

Nothing is known of the immediate etiology of these tumours, but their genesis is probably connected with a general hypersthenic reaction of the corticogenitalin system. In a case communicated by Van Kup, the autopsy of a boy with pubertas præcox showed a neoplasm of the adrenal cortex, hypertrophy of the pituitary and hypotrophy of the pineal.

Primary pituitary adrenal virilism is determined by an antepituitary adrenotropin-secreting tumour, a basophile adenoma. This physiopathological form is rare because most basophile adenomas secrete many hormones besides corticogenitalin and thus give rise to a more complex disease, Cushing's disease, and rarely to simple virilism.

Cerebro-pituitary adrenal virilism is determined by a total hypersthenic reaction of the cortigenitalin system beginning at the diencephalon. The abnormal hypersthenic diencephalic impulse causes hypersecretion of adrenotropin from the antepituitary basophile cells (manifested morphologically in some cases by hyperplasia of these cells), and this in turn stimulates the cortigenitalin-secreting cells, which also often become hyperplastic. The etiological conditions determining cerebro-pituitary adrenal virilism are not well known. An abnormal genogenic lability of the cortigenitalin system has been accepted, explaining the hereditary and familial incidence of the disease. Various factors, such as encephalitic localisations, other endocrinopathies mainly hypogonadism, and even psychogenic factors, affect the diencephalic centre of this labile cortigenitalin system, and promote development of the disease.

The Complete Form. A virile habitus in a woman is the essential presenting symptom. The body is straight and muscular, and has not the rounded shape with scanty muscular relief that characterises woman. The face is coarse and blunted, with striking beard, moustache and acne. The thorax is muscular, with breasts of male rudimentary type. The pelvis lacks female rotundity in contour and width, and assumes the narrowness seen in man. The feminine genu valgum is replaced by the masculine genu varum producing the characteristic straight parallel legs. The hair follows male distribution of scalp hypotrichosis, face and body hypertrichosis and triangular pubescence, and often exaggerates this distribution to the point of hirsutism. On the limbs it grows more on the extensor surfaces and more profusely on legs than arms. The texture is rough and coarse as in the male, lacking female silkiness. Muscles are well developed, and such women often show considerable muscular activity and indulge in sports. The prowess of some women in sports is often due to adrenocortical hyperfunction.

Sexually hypomenorrhœa and amenorrhœa are constant, indicating the defeminisation of the sexual system. The external genitals, tract and gonads are distinctly female but hypoplastic, another sign of defeminisation. The

clitoris, however, is frequently hypertrophic, a sign of distinct masculinisation.

Libido varies, as it is due to psychogenic as well as endocrine factors. In one series of cases it is of male type. This occurs not only in cases of intense morphological virilisation but principally in women showing mild morphological virilisation—a fact demonstrating the importance of psychogenic factors. In another group of cases libido is of female type and such women lead happy married lives. Finally, many virilised women lack libido entirely. This may be because the intersexual process has been sufficient to defeminise the libido but not to push it into masculinisation. However, psychological factors are preponderant in such cases, recalling the motto of the Rohans: "King I cannot, Prince I deign not, Rohan I am."

Psychological features arise either from the masculinising process, mainly endocrine, or from the patient's reaction to her abnormality. Those referring to the masculinisation are the most characteristic and show very early in the disease. Feminine charm and submissiveness are gone. Their place is taken by a male dominating character with features of leadership, manifested in the walk and dress of these women. Combativeness is marked, and when exaggerated makes viragos of them. They adopt male occupations, and on a higher plane show the male creative intellect instead of the feminine imitative intellect. With remarkable intuition Nietszche wrote: "When women achieve something great in science there is something wrong with their sexuality."

Psychological features derived from the psychogenic reaction of these patients to the masculinising process consist in various psychoneurotic and psychotic manifestations. They seem more marked in cases of mild morphological virilisation and should be borne in mind by neurologists. They take the form of withdrawing from social life, of depression which may lead to suicide, and of certain anti-social complexes. An endocrine factor is added to the psychogenic reaction, as demonstrated by the cure of real psychosis in virilism through adrenalectomy (Broster, Allen and their co-workers).

Urinary examination shows an increase of androgens, as shown first by L. Simpson. Dingemasse and Laqueur find 75–150 international units per litre in non-neoplastic cases, 600–2,200 in neoplastic cases (normal findings are 10–50). Œstrogens also are increased, pointing to the adrenocortical origin of certain œstrogens. The androgen-œstrogen ratio is characterised by a predominance of androgens as in men. Jocelyn Patterson and Allan Greenwood find in the urine a "free male hormone" (the androgenic substance extracted without previous hydrolysis of the urine), which has been identified chemically by Marrian as a special androgen unrelated to testosterone and thus probably of adrenocortical origin. This androgen is absent from the urine of normal women, and in women suffering from virilism diminishes after adrenalectomy and even disappears from the urine. Whenever this androgen was present the gland showed a special reaction described by Vines as fuchsinophile reaction. The 17-ketosteroids (not synonymous with androgens) also are increased, particularly in neoplastic cases.

Evidence of an adrenocortical tumour is apparent clinically in many cases but principally radiologically.

The subsequent history depends on the etiology. Neoplastic cases, if untreated, run a chronic and progressive course, and the end depends on the development of the adrenocortical neoplasm. This is of low malignity but in many cases initiates cachetic symptoms which cause death. The tumour is prone to extend into the adrenal veins and on the left side through the renal veins into the inferior vena cava. Secondary growths occur into the liver, lungs and lymphatic glands, sometimes exclusively in the brain (Devic and Dechaume). Bone metastases are rare, in contrast to their frequency in hypernephroma. Operated cases run a more benign course, the symptoms of virilism disappearing but reappearing if metastases occur, this time accompanied by general cachexia terminating fatally.

The other etiological forms of adrenal virilism proceed less severely although essentially chronically. In many cases œstrogenic treatment improves the condition. In severe cases adrenalectomy is beneficial (Broster). In untreated cases the condition persists as a disfigurement. It may lead to mental disturbances through consciousness of the disfigurement but does not shorten life.

Formes Frustes. The Amazonic form is a mild form of virilism lacking the repellent aspect of the complete form but, on the contrary, exhibiting a certain elegance. These women excel in sports and other male activities and show qualities of leadership. Their physique is mildly but elegantly masculininised, the facial expression definite and energetic, the body muscular and resilient, the gait steady. There is a certain tendency to homosexuality, usually manifested by incompatibility in marriage. Such women are often admired physically as well as mentally, although like the historical Amazon, Lady Hester Sharpe, " they do not arouse tender sentiments."

Female transvestists constitute another forme fruste of adrenal virilism. In them the feminine love of brilliant female clothing and adornment and careful make-up does not exist, and the simpler male clothing is preferred. Morphologically they show certain male features in the definite expression of the face, the muscularity and resilience of the body, the steadiness of the gait. Intellectually they are of the male creative type (the painter Rosa Bonheur, the writer George Sand). Libido is often homosexual, and even the male lovers of these women are feminised men, as were Alfred de Musset and Chopin in the case of George Sand.

Menopausal virilism is an interesting variety of this disease. Towards menopausis the adrenotropin-cortigenitalin system may react with hyperfunction to the involutional hypo-ovarism. The woman assumes a hard and masculine expression. Hair appears on the face. The voice becomes rough and the temperament domineering (mother-in-law type).

Therapeutics. In the rare cases in which an adrenocortical virilising tumour is diagnosed surgical removal is indicated. The immediate results are

often remarkable but relapses occur.

In the majority of cases, where the condition cannot be definitely distinguished as a primary adrenal or neoplastic virilism, a cerebro-pituitary adrenal virilism or even a basophile adenoma adrenal virilism, internistic treatment based principally on œstrogenic hormones should first be given. Results in mild and incipient cerebro-pituitary adrenal virilism are as brilliant as the surgical results in neoplastic cases, provided the patient collaborates and does not despair at the length of the treatment. Pituitary radiotherapy is a valuable adjunct. When œstrogens and radiotherapy yield no definite result and when the condition is very severe, surgical exploration is indicated. If an adrenocortical tumour is found, extirpation is followed by the results already described. If only adrenocortical hyperplasia can be detected partial adrenalectomy, introduced by Broster and the Charing Cross workers, can be performed; it yields some good results, probably through the same mechanism as thyroidectomy in Graves' disease. Here relapses are not to be feared but the danger of hypocortinism is greater.

Mildly virilised women are essentially worried by their facial hypertrichosis and acne. I have obtained good results in such cases from ointments containing œstrogens, combined with general constitutional and œstrogenic treatment. Electrolysis is sometimes a helpful local treatment of such hypertricosis but radiotherapy of the skin is dangerous.

The important role of general constitutional methods, psychotherapy in particular, needs emphasis.

Prognosis regarding therapy, including adrenalectomy, depend on whether there is a strong genetic " reactivity " element of the sexual formations. When such an abnormal reactivity plays an important part in the genesis of the endocrinism, endocrine treatment is of course less successful.

Ovarian Arrhenoblastoma Virilism.

The physiopathological basis of this condition is, apart from genetic reactivity, female testosterone hypersecretion originating in a special ovarian tumour, an arrhenoblastoma. The hilus of the ovary contains rudimentary testicular elements, evidence of the primary bisexuality of the gonad. For unknown reasons these elements can develop into a tumour, an arrhenoblastoma. Testosterone hypersecretion then occurs, giving rise to virilism. It is possible that such tumours originate in adrenocortical genital tissue included in the ovary in the course of development, and thus such virilisms can be regarded as linked physiopathologically with adrenal virilism.

Knowledge of this class of virilism is due principally to the work of Robert Meyer. The ovarian masculinising tumours responsible for it are usually unilateral and may reach a great volume. They are known by the generic name of arrhenoblastoma but their histological description is complex. Three types are described according to their relation with true testicular tissue. The first, a testicular adenoma, reproduces the testicular structure but without spermatogenesis. The second or intermediate type is further removed from

testicular tissue, although some tubules and cells resembling the normal testicular tissue are seen. The third or sarcomatous type is constituted of cells quite different from those of the testicle, although a clue to their origin is given by certain portions where cells are arranged in columns reminiscent of the sex cords of the early phases of testicular embryology. Besides arrhenoblastomas, other masculinising tumours of the ovary occur, such as luteomas (much debated) and adrenal rest tumours.

The clinical picture of this ovarian virilism is similar to that of the complete form of adrenal virilism, except that an ovarian instead of an adrenal tumour is detected. The course also depends on the neoplasm, which is of low malignity. Treatment is essentially surgical.

Both adrenal and ovarian arrhenoblastoma virilisms have to be differentiated from certain deep constitutional conditions of hypertrichosis.

CHAPTER XXXV

MAMMARY ANDROGYNOIDISM

(GYNECOMASTIA)

This constitutional disease is characterised essentially by the presence in a male of a mammary gland of female type. It was first described by Paulos of Aegina in the eighth century. By this term two different conditions of common intersexual origin are described, true gynecomastia consisting in real female gland with ducts and, exceptionally, with acini, and adiposomastia, in which the glandular tissue is rudimentary but fatty tissue is abundant on the breasts as in the female. The two often coincide.

Deep Constitutional Gynecomastia. Disturbance of the genetic constitutional regulators causes a peculiar reactivity of the cells constituting the mammary gland. They become more sensitive to œstrin, to which male cells are not sensitive. Such conditions are often hereditary and familial.

Gynecomastia is the only symptom. The individual is perfectly normal otherwise, and in particular shows no symptom of testosterone deficiency. His only abnormality is the possession of female breasts of varying degrees of development. Very often only one breast is of female type, this unilaterality giving a distinct genetic stamp.

Nosographical classifications on the basis of physiopathology are never absolute. The genetic factor of special reactivity exists in all forms of gynecomastia, and in many deep constitutional gynecomastias a hormonal element may contribute. Classifications are based only on preponderance of a particular physiopathological factor.

Treatment when cases are sufficiently advanced is exclusively surgical.

The Emile Laurent Syndrome. In 1894, Emile Laurent described a new syndrome, the association of bilateral gynecomastia with testicular atrophy. Klinefelter has recently made a more complete study of this condition.

It is characterised by (*a*) a bilateral gynecomastia, usually occurring after

puberty. The breasts resemble those of a normal female but there is no secretion. There is some hyperplasia of the duct epithelium and very marked proliferation of the periductal connective tissue; (*b*) small testis with aspermatogenesis but normal or only slightly reduced function of the Leydig cells; (*c*) normal development of the secondary male sexual characters, in particular normal growth of phallus, of prostate and of sexual hair; (*d*) increased secretion of alpha-gonadotropin in the urine (as in castration), reduced secretion of 17-ketosteroids, no evidence of increased excretion of œstrin. Klinefelter explains this gynecomastia by maintaining that in such cases the gametogenic testicular hormone inhibin is lacking, and thus testosterone, which has been shown experimentally to stimulate the growth of the breast (Selye), acts unchecked.

Transitory Gynecomastia of Male Puberty. This, the so-called adolescent mastitis, is often unilateral and determined by the endocrine imbalance of puberty, by a change in the œstrogens: 17-ketosteroids ratio in favour of œstrogens (Nathanson).

Adrenal Gynecomastic Feminism. This is a rare disease, of which only six cases have been described. It is characterised by the presence in a male of gynecomastia connected with an adrenocortical carcinoma. The gynecomastia reaches the stage of lactation. It is accompanied by other symptoms of demasculinisation, particularly by loss of potency and sexual feeling, and even by symptoms of feminisation such as female hair distribution and pigmentation of the linea, the latter reaching in a case of G. Holl " a degree only seen in pregnant women." Treatment consists in the removal of the adrenocortical tumour, and in Holl's case this resulted in the retrocession of gynecomastia and of other intersexual features.

The accepted physiopathology is hypersecretion of the cortilactin factor of adrenocortin and also of adrenocortical œstrin. Excess of urinary œstrogens was found in a case by S. L. Simpson.

The Symptomatic Gynecomastias. Gynecomastia constitutes part of the general picture of various diseases.

Testis Diseases. Gynecomastia is frequently encountered in interstitial tumours of the testis. It is seen also in chorionepithelioma of the testis and in extra-testicular chorionepithelioma. It has been described also following orchidectomy and X-ray treatment for testicular teratoma.

The hormonal imbalance mechanism which causes gynecomastia in such cases is not known.

Gynecomastia in Hepatic Diseases. Gynecomastia is encountered in some cases of cirrhosis of the liver. The accepted mechanism is that of male hyperœstrinism resulting from failure of the diseased liver to exert its normal œstrin-neutralising function.

Therapeutic Gynecomastias. Gynecomastia has been provoked in eunuchoid patients treated with testosterone (McCullagh) and in an Addisonian patient treated with massive doses of adrenocortical hormone (Edwards and others).

Gynecomastia in Acromegaly. This is determined by hypersecretion of the mammogenin-prolactin factor of the antepituitary, a factor secreted by the eosinophile cells of the anterior pituitary. Like its adrenocortical counterpart, this gynecomastia reaches the stage of lactation.

The cases of male lactation that delighted the teratological tastes of our fathers probably belong to this group. It is difficult to separate fact from fancy in these old observation. Costelar of Madrid reported in 1798 the case of a workman who gave the breast for five months to one of his twins because his wife had not sufficient milk herself. More recently Krafft-Ebing has told of a passive male intersexual whose breast secreted milk which was sucked by his lover. This observation provides a strong link between gynecomastia and other intersexual conditions.

CHAPTER XXXVI

MALE HERMAPHRODITISM

(GENITAL AND GONADAL ANDROGYNOIDISM)

Male hermaphroditism represents a high degree of intersexualisation, viz., feminisation in the male, the feminisation involving the morphological, psychological, and principally the genital sexual characters (male genital hermaphroditism or genital androgynoidism), or the morphological, psychological and principally the genital and gonadal sexual characters (male gonadal hermaphroditism or gonadal androgynoidism). In a previous work I have shown that the terms pseudo- and true hermaphroditism must be discarded because they perpetuate an erroneous conception derived from the demonological ideas of the ancient Eastern peoples.

This disease was described first by Pliny on the basis of speculations arising from old demonological notions and not from direct observation. He accepted the bisexuality embodied in these notions and in the statues shaped by the Greek sculptors as an expression of the legend of Hermaphroditos. Renaissance physicians such as Paolo Zacchia, Caspar Bauhin, Ambroise Paré, described such cases from the teratological rather than the true clinical medical point of view. The jurist Ulpianus had introduced the conception of a predominant sex in hermaphrodites, and on this basis Ambroise Paré distinguished male, female and bisexual hermaphrodites. This conception persisted up to the end of the nineteenth century, and Edwin Klebs, summarising knowledge of the subject up to that time, described also male hermaphrodites which he called male pseudo-hermaphrodites, female hermaphrodites which he termed female pseudo-hermaphrodites, and undetermined or bisexual hermaphrodites which he called true hermaphrodites. In my Thomas Vicary lecture before the Royal College of Surgeons in 1941 I think I demonstrated that there are only two classes of hermaphrodites, *i.e.*, of extreme intersexes, male and female, and that a bisexual individual, an individual of undetermined sex (Klebs' " true " hermaphrodite) does not exist. The demonstration was made

both by the historical method, which showed the erroneous development of the ancient pre-Hellenic demonological ideas into the " true " hermaphrodites of our textbooks, and by the biological method, which showed the experimental production of intersexes of various degrees according to the intensity of the intersexualising (masculinising or feminising) process. Thus hermaphrodites are genetically either males or females.

Male hermaphroditism is a deep constitutional or genetic disease. In other words, the sex reversal has occurred in the genetic phase of the sex-formative impulse and not at the endocrine phase. The etiology of the genetic disturbance is that of gene mutation in general.

Two forms can be distinguished according to the severity of the intersexualising process; the first degree or genital male hermaphroditism (the old male pseudo-hermaphroditism) in which the genital organs are more or less feminised but the gonads are male, and the second degree or gonadal male hermaphroditism in which feminisation bears also in part on the gonads.

Male Genital Hermaphroditism or Genital Androgynoidism.

A male genital hermaphrodite (genital androgynoid) is a genetic male in whom the intersexualising process has involved the morphological, psychological and principally the genital sexual characters but has spared the gonads, which remain male.

Genital male hermaphrodites or genital androgynoids have an external habitus in which either male or female morphological features predominate. Their male or female appearance is usually not distinct. They may look like women, with flowing facial contours, absence of beard or moustache, developed breasts, broad hips and swinging gait, or they may look like men. There is no absolute rule in human intersexualisation. According to conditions of reactivity the intersexualisation may bear on one or another group of sexual characters. The voice may be of male or female type.

The condition of the sexual system gives the precise stamp to the disease. Morphologically a mixture of male and female characters is apparent. Gynecomasty is present. The penis is small, under-developed, and resembles a large clitoris. The urethra opens below the penis instead of forming a closed canal within it and does not follow the entire inferior aspect of the penis. The urethral borders or folds, which thus fail to unite, develop into labia minora. In some cases the urethra opens in mid-perineum on the female pattern. The scrotum may be divided (bifid scrotum), forming labia majora which may or may not contain testes.

The genital tract also may be feminised, and thus vagina, uterus and tubes may exist in various degrees of development. All these anomalies exist in varying combinations. Incomplete forms of the disease show feminisation of the external genitals only, these individuals being thus hypospadiacs. In the complete forms the genital tract is feminised.

An accurate anatomical or surgical investigation shows that these individuals have male gonads, which are often not developed. No trace of ovarian tissue if found.

Menstruation, of course, does not occur. When the vagina is more or less developed, intercourse of female type can be accomplished.

The general psychology of these subjects is also a mixture of male and female features. It is usually predominantly male, and such androgynoids cling to their masculinity. Libido in particular is generally male. These subjects are attracted to women, and have been known to marry as women. The form of libido does not always correspond to the habitus. Some androgynoids of male habitus have a female psychology, and vice versa. True ambivalent libido does not exist. Some androgynoids are enabled to act sexually as man and as woman by possession of a vagina as well as a penis, but in careful observations it has been noted that intercourse with women is more pleasing to them. The possibility of both male and female intercourse does not mean ambivalent libido, and the physician can be misled by the boasting and showing off of these patients. Some androgynoids lack libido as well as potency, the intersexualising process having inhibited male sex development in this respect without promoting the corresponding female sexual character. Biological experiments provide examples of this mechanism.

Mental features are often complicated by psychoneurotic or psychotic manifestations. These are essentially psychogenic and due to the reaction of the patient to his peculiarity. They may take a violently anti-social character or depression may predominate. Suicides have been reported, particularly when such individuals have been forced into the female sex.

Course of the disease. The disease exists at birth, and inspection at that time of the external genitals gives no basis for registering the infant as of a definite sex. In doubtful cases the registration is male and subsequently the infant is reared as a male.

As the years pass, and particularly after puberty, the intersexualisation becomes more manifest and is fixed for life.

Ancient authors have described as " changes of sex " states which can be considered as retrocessions of androgynoidism, and are always from female to male. The remasculinisation bears chiefly on morphological and psychological characters. To such an occurrence Ambroise Paré referred in his story of Germaine Marie, a " girl " who at the age of 15 leapt over a stream while running after her pigs and to " her " horror saw male genitals. And Montaigne adds that a song became current in that region warning girls against jumping too high. A much more precise observation comes from Raoul Blondel. It was the case of a married " woman," whose marital life was happy although she knew that she could never have children because she had never menstruated. Intercourse was possible, but difficult, because her vagina was small (3 cm.) and during intercourse she had erections of the clitoris (in fact, a hypospadic penis) and ejaculation. Libido was of distinctly female type. At the age of 45 " she " fell from a height of 13 feet, after which accident two " glands " descended into the labia majora and were demonstrated to be testes with epididymis and vasa deferentia.

Such cases, however, are neither changes of sex nor retrocessions of the

disease. They represent simply a correction of cryptorchidism, which is one of the elements of the disease but not a causal factor. The testis may descend but the basic disease continues. In young subjects the descended testis functions more normally as regards secretion of male hormone, but this is not sufficient to change the morbid process.

Male Gonadal Hermaphroditism or Gonadal Androgynoidism. A male gonadal hermaphrodite (gonadal androgynoid) is a genetic male in whom the intersexualising, viz., feminising process has involved to a varying degree the morphological, the psychological, but principally the genital and gonadal characters. This nearly complete feminisation of a male involving the gonads has been reproduced experimentally. The description of gonadal male hermaphroditism is difficult because built on observations of individuals showing a mixture of male and female morphological, psychological and sexual features but possessing both ovarian and testicular tissue. These individuals thus cannot be labelled as genetic males feminised to a high degree or genetic females masculinised correspondingly. To avoid this dilemma the will to sex, *i.e.*, the pragmatic and not the genetic sex, is taken as guide. In other words, the clinical history of gonadal male hermaphrodites is based on observations of those individuals, hitherto described as " true " hermaphrodites or cases of undetermined sex, who possess both testis and ovaries and the will to be males.

The morphological features are usually of female type. The psychology, however, is mostly male—probably as a reaction, a sort of masculine protest maintaining virility, especially as these patients will to be males. The voice is of female type.

The genitals usually show intense feminisation as in the genital form of hermaphroditism. Vulva, vagina, uterus, tubes and female breasts develop to varying degrees with parallel under-development of the male genital features. The penis is hypospadic.

The testes and ovaries coinciding in these patients may be completely developed glands, as in the case of Urechia and Teposu, but are usually undeveloped or one at least is rudimentary. They may be separated or united in an ovotestis. The ovary can be detected only at operation or autopsy. A testis can often be palpated in a more or less rudimentary scrotum. An interesting variety is represented by Lindval-Wallgren's case, in which a testis was present on the right side and an ovary and tube on the other, the uterus inclining more to the left. Such cases correspond to the gynandromorphs of the zoologists, birds male on one side and female on the other.

Menstruation may occur in such individuals. The co-existence of penis and vagina allow of intercourse with both men and women, but intercourse with women is more enjoyable (case of Karl Hohmann). Libido is, in fact, of male type. One of the most celebrated gonadal hermaphrodites, Karl Hohmann, married and his wife had a son whom she attributed to him.

As already indicated, the will to sex is male.

Diagnosis. The important diagnostic point is determination of the maleness or femaleness of the hermaphrodite, *i.e.*, determination of the genetic sex. This is clinically possible in some mild cases of genital male hermaphroditism, particularly by inspection of the external genitals. In many cases it is impossible, and guidance must be invoked from the pragmatic sex, *i.e.*, the sex willed by the patient.

The rationality of this procedure is demonstrated by (*a*) the failure even of complete surgical or anatomical investigation to determine the genetic sex of complete hermaphrodites, as they have both testis and ovaries; (*b*) the misery and even suicide of hermaphrodites forced into a sex which they do not desire; (*c*) the safe guidance of the pragmatic sex, as shown in an observation of Young, in which a patient brought up as a boy was discovered at the age of seven to have a vagina and tubes and a gland resembling an ovary. His status was changed and a penis, taken for a hypertrophied clitoris, amputated. Later a testis was discovered and excised, but no ovarian tissue existed. The patient, however, wanted to be a male, and in fact he was genetically male. He assumed male status when he came of age, found employment as a lorry driver and lived apparently happily as a male without penis or testicles but with a vagina.

Acceptance of the pragmatic sex as a basis of classification is, of course, indicated only for severe hermaphrodites and not for morphological or psychological male intersexes, nor even for mild genital hermaphrodites. In mild cases the genetic sex is very apparent, and certain social factors enter into consideration. Each case must be considered by itself.

Determination of sex on the basis of the will of the patient is possible only when the patient is able to decide, but of course impossible in early life. The following is the most practical procedure. In cases of great difficulty, when inspection of the external genitals gives no guidance, male hermaphroditism is diagnosed and the infant reared as a male. He can change his status when he reaches the age of sex consciousness except if definitive objective findings fix him as a male. The original diagnosis is justified by the fact that most cases of clinically doubtful sex are genetically male. These individuals are sent to boys' schools, and if by chance they are female hermaphrodites the mischief is not great. Theoretically they can be violated but practically speaking this never happens as they never attract attention by their abnormalities. Their large clitoris passes for a penis and their vagina, particularly before puberty, is totally undeveloped and masked by incomplete union of the labia. If male hermaphrodites are placed in a girls' school, however, they can act sexually as males and deflower their girl companions. It is obvious that physicians must exercise great care in advising on the registration of intersexes.

Therapeutics. General constitutional measures, educational measures and, principally, psychotherapy are of great importance. Guidance of such individuals by an internist endocrinologist is absolutely indicated.

The basic treatment is surgical, plastic procedures aiming at perfecting the

male sex. Brilliant results are often achieved, as cited in the works of Hugh Hampton Young and of L. Ombredanne, and these patients are directed into a more or less normal life.

The utmost care is necessary in removal of the gonads. The haphazard removal sometimes practised is useless vandalism and makes castrates of such patients. When a hermaphrodite wants to be a male and has ovarian tissue, this can be removed. If he chooses the female sex, orchidectomy can be performed, even though the effects of this procedure are problematic as the testes of male hermaphrodites secrete great quantities of œstrin. It has been noted that after orchidectomy in such cases severe " menopausal " symptoms have followed, unrelieved by testosterone propionate but improved by œstrogens.

CHAPTER XXXVII

FEMALE HERMAPHRODITISM

GENITAL AND GONADAL GYNANDROIDISM.

Female hermaphroditism is a constitutional disease characterised by intersexualisation in a female (thus, masculinisation) of the genital and gonadal sexual characters. When only the genital features are masculinised the individual is a female genital hermaphrodite; when both the genital and the gonadal characters are masculinised the result is a female gonadal hermaphrodite or gonadal gynandroid.

Whereas male hermaphroditism is always a deep constitutional disease, female hermaphroditism is either a deep constitutional or an endocrine disease. Gonadal female hermaphroditism is always deep constitutional. In this disease sex reversal has occurred at the genetic phase. Female genital hermaphroditism is either deep constitutional or endocrine adrenal. In the adrenal forms the physiopathological basis is a congenital adrenocarcinoma or a congenital adrenal hyperplasia which arises from a primary developmental defect of the adrenal cortex.

Female Genital Hermaphroditism or Genital Gynandroidism.

The etiological constellation of the patients shows no special feature except sometimes a familial or hereditary incidence.

The etiological constellation of these patients shows no special feature except sometimes a familial or hereditary incidence.

The post-natal development is often characteristic. In some cases these individuals resemble little boys so much and have so many male genital features that they are reared as boys. Usually the female sex is more apparent at birth but progressively masculinisation develops with tallness, muscularity and pilosity. Menstruation either never occurs or stops very soon. The voice breaks and becomes masculine. These children spurn girlish games and like other virile sports.

The adult habitus is that of a man—muscular, straight, with well-marked hair on face and body and little on the head. The breasts are rudimentary, *i.e.*, of male type. The pelvis, however, is usually broad, *i.e.*, of female type.

Mentality is virile. Some of the few married female hermaphrodites have practised virile professions and undertakings.

The genitals show various degrees of masculinisation. The clitoris is hypertrophic to the size of a penis, often with glans. The urethra may open at the perineum but in most cases is partly masculinised, forming an open groove following the inferior surface of the penis-clitoris (female hypospadias). In some exceptional cases such as that described by Ombredanne, the urethra is masculinised completely and takes the form of a closed canal opening in a meatus at the glans of the clitoris-penis. A prostate has been described from hypertrophy of the male prostatic rudiments existing in the female (Johnson). Epididymis and vas deferens have not been observed in female hermaphrodites.

The labia minora retain their female aspect, except in rare cases when they constitute urethral folds on each side of a hypospadic urethra or even unite to close the urethral groove, thus forming a male type of urethra. The labia majora also retain female features, except that they join to form a scrotum. A vagina exists, opening either at the perineum or in the urethra. Uterus and tubes are normal except that, like the vagina, they may be undeveloped owing to the masculinising process.

Libido in mild cases may persist in female type but in more accentuated female hermaphroditism it is distinctly masculinised. Many of these women have satisfactory intercourse with other women. They experience erections, ejaculation (probably from the prostate) and orgasm. Some of them marry as " men " and their sex may be detected only at autopsy.

The will to sex may be towards femininity in mild cases, but in more accentuated conditions it tends to masculinity. Tragedies, even suicides, have occurred when these individuals have been thwarted in their will to maleness, for instance, when they have not been allowed to marry the girl they had chosen.

The course of adrenal neoplastic female genital hermaphroditism depends on the neoplasm, and is short. The course of female genital hermaphroditism from adrenal hyperplasia is much longer, and a few of them have lived happily as married or unmarried " men." The course of deep constitutional female genital hermaphroditism resembles that of the adrenal hyperplastic form. In all these forms, but particularly in the last two, psychoneuroses and psychoses may develop, either through consciousness of the disfigurement or because of frustration in the will to masculinity.

Female Gonadal Hermaphroditism or Gonadal Gynadroidism.

The clinical history of this severe form of female intersexuality is gathered from observations of individuals possessing testis and ovaries but showing a will to femininity.

The clinical picture resembles that of male gonadal hermaphroditism

except for a greater number of female morphological features and the will to femaleness.

The gonadal features in particular are a mixture of male and female in various proportions. In extreme cases separate ovaries and testes are seen. In moderate cases the gonad or gonads are formed of ovarian and testicular tissue (ovotestis). In other cases, such as that described by E. Witchi and W. F. Mengert, the gonads appear as testes, but their structure is peculiar in that follicles are found in the testicular tissue. Œstrogens are sometimes found predominating. Menstruation may occur but is rare. Libido is usually absent.

Diagnosis and Treatment. These follow the lines described for male hermaphrodites. I do not believe that adrenalectomy is indicated in these cases.

CHAPTER XXXVIII

ADDISON'S DISEASE

Physiopathology and Etiology. Addison's disease is a symptom-complex constituted mainly of asthenia, melanotic pigmentation, hypotension and digestive disturbances connected with an adrenal, principally adreno-cortical, hypofunction. The special adrenal physiopathology isolates the disease as a nosographical entity.

It was first described by Thomas Addison, one of the great men of Guy's, who gave the complete clinical picture as well as the physiopathological adrenal basis of the condition. In searching for the cause of pernicious anæmia Addison " stumbled," as he said, on the bronzed disease, and communicated his first researches in a paper " On Anæmia, Disease of the Suprarenal Capsules," read at the South London Medical Society on March 15th, 1849. Six years later he published his classic, " On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules." Addison's work marks not only the isolation of a nosographical entity but also the beginning of modern endocrinology. In 1856, Trousseau gave to this disease, for which Addison had proposed the term melasma suprarenale, the name Addison's disease.

The clinical chapter of the natural history of Addison's disease was written so completely by Addison himself that little was added until the early 'nineties, when Sergent and Leon Bernard, mainly, described non-melanotic forms and formes frustes. The physiopathology was debated for some time. A year after Addison's publication, Brown-Sequard confirmed the adrenal conception by his experiments on adrenalectomy. Many others, however, rejected this physiopathology and held that Addison's disease was related to lesions of the abdominal sympathetic. During the last thirty years, however, the adrenal conception has predominated almost exclusively, and has been proved, and localised mainly in the cortex, by experimental work.

In Addison's disease the essential constitutional regulator involved is the cortin system, which is in hypofunction. The hypofunction is due to a disturbance either of the glandular centre of the system or of the diencephalic centre. Secondarily to the cortin system the gonadal and thyroid systems are involved and are disturbed in their functions.

The cortin system being an important regulator of body chemistry, far-reaching metabolic disturbances occur in Addison's disease and explain the numerous systemic and organic deficiencies seen in this condition. Protein, carbohydrate, fat, electrolyte and water metabolisms are deranged. (To avoid repetition the details of these disturbances are given in the biochemical syndrome of this disease.) On these metabolic disturbances depends the rich symptomatology of the disease.

Primary or glandular hypocortinism is due in some rare cases to adrenalectomy or destruction of adrenocortical function by X-rays, but usually to a suprarenalitis. This is generally of tuberculous nature (80 per cent. of complete chronic cases) and is always secondary to another tubercular focus in the body. In rarer cases the suprarenalitis is due to syphilis, malaria and acute infections such as diphtheria, typhoid fever and scarlet fever. Toxic factors have been less thoroughly investigated. Cancer of the adrenals may exceptionally be an etiological factor. I have published distinct examples.

Cerebro-pituitary hypocortinism is probably more important in formes frustes, but is encountered also in more accentuated conditions. It includes the cases known as Addison's disease through " atrophy " of the adrenal cortex, met with increasing frequency. Atrophy of the adrenal cortex is in fact not the cause but the result of a deficiency of adrenotropic hormone, itself the consequence of a defective impulse from the diencephalon. Thanks to the work of Selye, combined with knowledge of the genetic biological inferiorities of the adrenocortin system, the mechanism of cerebro-pituitary hypocortinism has been well elucidated. Selye has shown that various non-specific stimuli such as traumatic and surgical shock, infectious diseases, burns, drugs, physical factors such as cold and functional nervous commotions such as rage and fear often elicit a phase of sideration or shock, followed by a reaction of the adrenocortin system which develops in three stages, a stage of counter-shock, a stage of resistance and a stage of exhaustion. The phase of sideration and counter-shock constitute the " alarm reaction." The stage of exhaustion of the adrenocortin system is a hypocortinism involving thus the whole adrenocortin system, a cerebro-pituitary Addison's disease whose clinical development varies according to the biological capacities of the adrenocortin system. The syndrome described by Selye is the syndrome of adaptation of the individual to noxious non-specific stimuli. Cerebro-pituitary hypocortinism is thus a disease of adaptation.

Symptomatology. The Common Form.

The disease starts slowly, and its progress is often marked by tuberculosis of lungs, kidneys, or testicles. It is often ushered in by an inexplicable asthenia and languor, more mental than physical at first and thus mistaken

for a "nervous breakdown." In other cases digestive disturbances, indigestion, constipation, nausea and vomiting are the initial symptoms, and such patients consult gastroenterologists. In rarer cases it is the skin pigmentation which is most striking at onset, or a progressive and inexplicable loss of weight.

General Symptoms. The most important are pigmentation of the skin and mucosæ, and loss of weight, asthenia, mental depression, hypotension.

Morphological syndrome. The skin pigmentation is melanotic, the general coloration being sun tan, a mulatto tint or, rarely, an olive tinge. It is diffuse but more often marked in certain regions while absent from others. It is deepest in normally pigmented regions such as the mammary areoles, pubis, external genitals, axillæ, in places exposed to light such as face, neck, dorsum of hands and the ears, and in places exposed to trauma such as the girdle region, elbows, knees, scars of wounds, burns and vaccination marks. It is less noticeable in covered and protected parts, and is absent from the palms of the hands and, save in exceptional cases, from the nails. Depigmented areas of leucoderma may co-exist. Mucous membrane pigmentation is constant in the mouth, and is characterised by melanotic plaques varying from small specks to patches 2 cm. in diameter irregular in contour but with well defined edges. The lips are dark, especially about the corners of the mouth. Palpebræ and, exceptionally, teeth are pigmented. The pigment is contained in the deeper cells of the epidermis and is chemically a melanin, although some authors have found the reaction of iron.

Loss of weight is intense and rapid, and may amount to 5–6 stone in adults. It is due to disappearance of fat and intense muscular atrophy. Despite the loss of weight, however, the skin conserves its elasticity and thus has not the flabby appearance characteristic of other wasting diseases.

Mental and nervous syndrome. Asthenia is prominent. It is marked even in early cases, and for a long time may be the only symptom. In many cases it is characterised by intense exhaustion after slight physical effort, such as occurs for instance in the morning routine of dressing, which the patient notes as becoming more and more difficult and strenuous. In more advanced cases it is a chronic fatigue, patients feeling tired mentally and physically throughout the day but showing also paroxysmal attacks of exhaustion verging on collapse. In the advanced cases the patient lies in bed and shuns all movement, even deglutition.

Mental depression, discouragement and apathy are parallel with the physical weakness, and colour the whole psychology of Addisonians. Mental depression may be pronounced before either physical asthenia or muscular atrophy sets in, occurring independently of other symptoms and leading some physicians to assure such patients that "the trouble is all in the mind." It takes the form of defective cerebration, amnesia, lack of concentration. Patients avoid both mental and physical effort because mental effort causes the same feeling of fatigue. Courage and will power are notably lacking.

adding to the incapacity for action—the adrenal has been called the gland of courage. Apathy is marked in advanced cases, being such that patients take no interest in their surroundings or even in important family events. Much less often anxiety and irritability are seen. It is a " faiblesse irritable," to use the French clinical term, such patients being full of complaints, exacting in their demands, difficult to satisfy, apprehensive, grasping at relief.

Sleep is disturbed in parallel with the physical and mental asthenia, with daytime drowsiness and nocturnal insomnia. It is characteristic of Addisonians that sleep overcomes them at any time of day. Night sleep, however, is restless with incessant tossing and frequent wakings.

Psychotic manifestations sometimes develop. Incompetence, disorientation and confusion become manifest. A patient of Rowntree had definite delusions of persecution which persisted for several days until his physical condition had distinctly improved. Hallucinations and delusions of sight and hearing may develop (Cawadias).

Reactivity syndrome. Thermic reactions are frequent, and are explained by the disturbance of heat regulation in adrenal hypofunction. Addisonians cannot tolerate excesses of temperature, particularly of cold. In some cases the central temperature is low but attacks of hyperthermia have been noted.

Sensitivity to narcotics is marked, and cases have been described in which Addison's disease has started after operation. This sensitivity is the source of the great danger of operations on Addisonians. Sensitivity to barbiturates has been described by Thaddeus. Sensitivity to solar irradiation is great and important, because in mild undiagnosed cases patients exposing themselves to sunlight for tonic purposes are liable to severe accidents and even death. Defective resistance to infections has been observed clinically and confirmed by experimental work. Sensitivity to insulin is outstanding and due to the Addisonian hypoglycæmia, which manifests lack of the adrenocortical hyperglycæmic factor while insulin secretion remains normal. Any excess of insulin thus causes hyperinsulinism. Such patients must never be given insulin " to improve the appetite and nutrition," and they are a grave warning of the danger of grasping reflexly at the insulin syringe for all cachexias.

Sexual syndrome. This is important in mild cases. Amenorrhœa or oligomenorrhœa may be the presenting symptom, and I have detected Addison's disease in some women consulting for such menstrual disturbances. Similarly, lack of potency and libido may be the presenting symptom in men. These manifestations are due to the general metabolic disturbance due to deficiency of cortin, not to lack of the sexual factor of the adrenal cortex, cortigenitalin, which does not appear to be involved.

Organ Symptoms. Digestive and circulatory syndromes. Anorexia is the most prominent digestive symptom, and varies from mere lack of appetite to intense loathing of food. Nausea and vomiting may occur independently. Nausea often occurs only before breakfast but in some cases lasts the whole day and even night. Vomiting often accompanies nausea, and in some cases

is as uncontrollable as the vomiting of pregnancy. Hiccough is also noted. Constipation is less prominent but more common than diarrhœa, which, however, predominate in some cases and may be so intense as to give the picture of cholera. Painful abdominal attacks may occur, in mild form simulating duodenal ulcer, the more severe taking the form of acute abdomen with vomiting, intense pain and retraction of the abdominal muscles. It is important to bear in mind all these digestive manifestations of the disease, as Addisonians often come first to the gastro-enterologist.

Hypotension is as characteristic of the disease as muscular asthenia. The systolic pressure is below 100, the diastolic below 70. When the patient rises from bed pressure falls even lower, as manifested clinically by vertigo and faintness. Exceptionally, cases with normal or even slightly raised pressure are seen, these probably being cases of previous hyperpiesia. Loss of venous and capillary tone accompanies the arterial hypotension. Tachycardia of mild degree is usual but is difficult to assess on account of the smallness of the pulse. Electrocardiographic changes of the heart have been described.

Rowntree and Brown have found diminution of the blood volume during Addisonian crises and in the terminal phases of the disease. Addison, who of course had no blood-counting apparatus, regarded anæmia as a constant symptom. The intuition of that great clinician was not wrong, but the anæmia of hypo-adrenalism is one of oxygen deficit and not of lack of erythrocytes, which are usually normal in number and sometimes even more abundant through the concentration of blood due to transudation of plasm, vomiting and diarrhœa. The existence of lymphocytosis and hyperplasia of the lymphatic system has raised speculation as to the hypoadrenal origin of status thymicolymphaticus.

Nervous paroxysmal attacks, mainly convulsions or petit mal, may occur on the basis of hypoglycæmia. They are not frequent, Addisonian hypoglycæmia usually being clinically latent, but the clinician must bear them in mind.

This clinical picture is often complicated by tuberculous involvement of various organs. Addison's disease is due in 80 per cent. of cases to tuberculosis, but adrenal tuberculosis is rarely primary. In most cases the primary focus is testis, epididymis, kidney or lungs, to which clinical attention should be directed.

The Biochemical Syndrome. The most important biochemical findings, indicating the metabolic disturbances caused by cortin failure and the coinciding failure of other constitutional regulatory elements, are:—

1. Diminution of basal metabolism. This is due to a coincident hypothyroidism.

2. Increase of urea and non-protein nitrogen in the blood. This is caused by disturbance of protein catabolism, cortin being a protein-catabolic hormone. According to many authors, however, it is caused by renal insufficiency, cortin being a regulator of renal excretion according to these same authors.

3. Presence of creatine in the urine. The mechanism of this metabolic abnormality is obscure but probably connected with the muscular weakness.

4. Hypoglycæmia and increased carbohydrate tolerance. These are linked with failure of the diabetogenic or anti-insulin function of cortin.

5. Lipolysis and thus wasting of the fat depots. This may be secondary to the disturbance in ionic equilibrium provoked by cortin deficiency, a disturbance reacting on all cell functions, or may be connected with failure of the (insufficiently demonstrated) fat-anabolic function of cortin.

6. Diminution of sodium chloride in the blood and increase in the urine, thus loss of sodium chloride. This is an outstanding metabolic disturbance, cortin being essentially a sodium chloride retainer in the body.

7. Disturbances in water metabolism. Diminution of the plasma volume due to shifting of water towards the tissues is demonstrated by the increase in erythrocyte concentration shown by the hematocrite. Additional intake of water is excreted with delay (Robinson, Power and Kepler's water test) but in the end there is water loss, as shown by the dehydrated appearance of the patient. This is bound up with the sodium chloride loss caused by cortin deficiency, sodium chloride being a powerful water retainer in the body.

8. Increase of potassium in the blood, *i.e.*, retention of potassium in contrast to loss of sodium chloride and water. Potassium is probably retained so as to re-establish the osmotic equilibrium destroyed by loss of sodium chloride, but its retention causes a great qualitative disturbance in the composition of the blood and plays a great role in the genesis of Addisonian symptoms.

9. Low level of vitamin C in blood and urine. The adrenal cortex stores vitamin C, and failure of this storage function causes impoverishment of the body in this vitamin.

Data regarding cholesterol are conflicting. It has been described as increased in the blood by some authors, decreased by others. Data regarding calcium also show conflict. Magnesium is retained in experimental adrenalectomy but findings in clinical Addison's disease are not distinct.

The alkaline reserve is low as a result of relative preponderance of Cl over Na and of renal insufficiency. This acidosis is probably responsible for the hyperpnœa of the terminal stages.

Course. The disease runs a chronic course interrupted by paraxysms, Addisonian crises, during which all symptoms, the asthenia and digestive manifestations in particular, are aggravated.

The average duration in tuberculous cases is a little over a year, in non-tuberculous cases about $2\frac{1}{2}$ years. There are, however, cases of much shorter and longer duration. The latter are usually non-tuberculous. About twelve cases have been observed as lasting more than 10 years, and it is probable that with progress in treatment prolongation will become more frequent.

The disease ends in sudden death, more frequently in coma, and in tuberculous cases in tuberculous generalisation.

The possibility of sudden death should always be kept in mind and brought

to the attention of the relatives. The end may come without any apparent reason, the patient feeling relatively well beforehand. In other cases it occurs as the result of a drug administration, a purgative, injection of an anti-syphilitic drug or a mild infection.

Special Forms.

The Major Acute Forms. These are the severe forms of Addison's disease. Their first description came from Sergent and Leon Bernard 40 years ago. The physiopathology and etiology offer certain peculiarities. The process involves cortex as well as medulla, principally the cortex. It is either suprarenalitis more or less distinct at autopsy, or a hæmorrhage or thrombosis of the adrenals. Suprarenalitis is determined by various infective factors such as diphtheria, typhoid, influenza, meningococcus, scarlet fever. It is also determined by such toxic factors as food poisoning, acute alcoholic intoxication, chloroform intoxication (which involves more the medulla) and the auto-intoxication of burns.

Hæmorrhage of the adrenals and thrombosis is probably a form of suprarenalitis. It is often accepted as a combination of venous thrombosis with an increased permeability of the vessels due to toxins from virulent micro-organisms. Typical hæmorrhagic suprarenalitis is encountered in meningococcy (Waterhouse-Friedrichsen syndrome), in various infections and even traumas such as surgical interventions on the adrenals. Suprarenal hæmorrhage may be due to other factors, however, and it is interesting to note that deficiency of pantothenic acid has caused experimental adrenal hæmorrhage (Daft and Sebrell).

Acute adrenal insufficiency independent of suprarenalitis occurs in certain cases of removal of adrenal tumour or of adrenalectomy, when the opposite gland is not sufficient to cope with the demands of the body for cortin. Surgical shock is considered by some authors as a manifestation of acute adrenal insufficiency.

An acute adrenal insufficiency may supervene through the action of these factors on previously healthy individuals, but in many cases it develops in persons with a latent hypocortinism, which is often encountered in children and described as status thymicolymphaticus. These are overweight children of pasty appearance, inclined to allergic reactions (Czerny's exsudative diathesis) with a large thymus and palpable lymph nodes. In such individuals the adrenal insufficiency remains latent thanks to the slow and progressive adaptation of the other neuro-endocrine systems, or through compensation by accessory adrenals. An occasional factor, however, may upset this unstable balance, and thus symptoms of adrenal insufficiency may manifest themselves suddenly and violently. This occasional factor varies. It may be an infectious disease, an acute tuberculous episode, a food poisoning, solar irradiation or, as described by Teissier and Sergent, anti-typhoid vaccination.

The clinical syndrome manifesting an acute adrenal insufficiency is characteristic principally when occurring in persons previously healthy in appearance. It consists in (*a*) Acute pain, para-umbilical or lumbar, usually

but not always without rigidity, and indicating the adrenal involvement; (*b*) Persistent vomiting with or without diarrhœa; (*c*) Dyspnœa of the air hunger type and restlessness; (*d*) Hypotension and cyanosis, and in general cardiocirculatory collapse, "shock"; (*e*) Hypothermia or hyperthermia, the latter due to a causal infection but also to the endocrinism; (*f*) Terminal coma. These symptoms occur in various degrees and combinations.

The clinical picture of major adrenal deficiencies varies, however, and for this reason the condition is often unrecognised. In many cases the clinical picture is that of an acute abdomen, a choleriform attack, meningitis, acute toxic delirium or coma. Cardiocirculatory collapse is outstanding. In one class of case the syndrome presents intense dyspnœa, restlessness and hyperpyrexia. This is called the pseudo-pneumonic form, but from what I have seen, restlessness is the dominating symptom. In other cases the only manifestation is sudden death occurring in perfect health, in the course of an acute infection, after surgical operation or following exposure to heat or sun. These sudden fatalities, which are those of status thymicolymphaticus, often present difficult medico-legal problems.

In the new-born, acute adrenal insufficiencies show certain special features studied by Goldzieher. They are due to a destructive hæmorrhage of the adrenals involving both glands. The general picture is that of a broncho-pneumonia with rapid respiration which may assume the Cheyne-Stokes form, hyperthermia, apathy, cyanosis and petechial rash. The abdomen is distended and boggy, sometimes acutely painful, and a mass in the renal region on one or both sides can be felt. There coincide signs of internal hæmorrhage. The blood chlorides and sugar fall and nitrogen rises (Goldzieher). Death with shock and collapse occurs in 24 hours, but occasionally may be delayed three or more weeks. Physiopathologically all symptoms bear the hypocortinic stamp except the rash and fever, which cannot be attributed to adrenal insufficiency but are probably due to the causal infection.

The clinical delineation shows the atypical nature of major adrenal deficiencies and thus the difficulty of diagnosis. The problem is even harder when they supervene in the course of an acute infection which masks the adrenal localisation. The clinician must think of acute adrenal deficiency in spontaneous conditions as well as in the course of an acute infection, and advise cortin which in such cases is often life-saving.

In my Paris days with the Leon Bernard group I was often astonished by the brilliance of such diagnoses from certain clinicians. On paper, recognition of acute adrenal deficiency seems hopeless. At the bedside the intuition of the clinician compensates the lack of specific signs, and this intuition is a very real factor. Furthermore, in our feverish quest for positive laboratory signs we may well have lost sight of the possibility of characteristic clinical symptoms as a help to diagnosis. Intuitive clinicians like Neusser, Ortner, and so tradition tells us, Oppolzer, made brilliant diagnoses by considering symptoms, and Ortner even detected errors to which absolute reliance on laboratory signs was leading. They based their procedure of diagnosis through

symptoms on their fine artistic sensibility, and their extensive memory of cases seen in the course of their experience. Ortner, with whom I came into contact, attempted a more systematic exposition of this symptomatological basis of diagnosis. Research on these lines would mark a great advance in our art.

The Formes Frustes. These are frequently cerebro-pituitary hypocortinisms. Their study began also in Paris with the Leon Bernard group. The usual form is the " neurasthenic form." These patients tire easily and their fatigability dominates the picture. They are well in the morning but as soon as they start any physical work they feel great fatigue, are " all done." Rest improves them, they think they can continue with their work, but again after the slightest effort they are forced to abandon it. They are sad, depressed and morose. Their blood pressure is low. They are thin, and notwithstanding a good dietary they accumulate no fat. They feel all changes of temperature acutely and have a tendency to anaphylactic shocks, particularly after receiving arsenicals and various vaccinations. In some cases the presenting symptom of these formes frustes is a menstrual disturbance, for which the patient seeks a consultation. Cortin improves these conditions greatly.

As already pointed out in the etiology, mental factors are important in the genesis of formes frustes of hypocortinism.

Various conditions have been described as oligosymptomatic forms of hypocorticoadrenalism. A certain number of myasthenias have this origin. Sea-sickness seems based in some cases on adrenocortical insufficiency, and the same can be said of some cases of vomiting of pregnancy and cyclical vomiting in infants.

Diagnosis.

This is far from easy, especially at the time of onset, during which the only presenting symptoms are asthenia and digestive disturbances. The difficulty becomes greater when Addison's disease supervenes in an individual already suffering from a tuberculosis in an organ other than the adrenals, and in such cases asthenia, hypotension and digestive disturbances are often taken for a simple exaggeration of the general symptoms of tuberculosis. This pitfall can be avoided by those who, remembering Addison's disease, look for certain more specific symptoms such as intense and intractable anorexia, hypotension, pigmentation and the biochemical findings of Addison's disease.

One of the most important pitfalls in diagnosis of Addison's disease is the following. Many patients who show asthenia and dyspeptic disturbances are being labelled neurasthenia, anæmia, rheumatism, nervous dyspepsia, and such patients prove later to be suffering from Addison's disease. All these are false diagnoses, for none of these terms represents a real disease but merely symptoms. The pitfall is avoided by those who are not satisfied by the words neurasthenia, anæmia, rheumatism and nervous dyspepsia, but who look for diagnosis of a real disease. It is avoided also by those who think of Addison's disease in such cases and seek for the more specific symptoms, " generals " and " biochemicals " of Addison's disease.

Cancer of the stomach and cancer in general offer a frequent and difficult

diagnostic problem. Diagnosis is based mainly on the radiological findings for cancer of the stomach, and on the "generals" and "biochemicals" of Addison's disease. From the purely clinical point of view nausea and vomiting are more intractable in Addison's disease and do not occur in cancer of the stomach except at an advanced stage, at all events in such intensity. Hypotension and anorexia are more marked in Addison's disease, and the melanodermic pigmentation of adrenal insufficiency can usually be clearly differentiated from the pale hay colour of cancer.

Myasthenia gravis also presents some difficulties of differentiation from Addison's disease. In myasthenia gravis, however, the ptosis and weakness of the muscles of the cheeks and lips impart to the face a very characteristic appearance. The speech is more often disturbed than in Addison's disease, such patients speaking first a few sentences with perfect distinctness but lapsing into progressive indistinctness until they are wholly unintelligible. The electrical myasthenic reaction may also help diagnosis. However, differentiation of such cases from Addison's disease without pigmentation is often very difficult, especially as Addisonians show the same basic muscular disturbance, easy fatigability, so much so that many authors have considered myasthenia gravis as a manifestation of hypoadrenalism.

Cases of Addison with pigmentation are usually easier to differentiate. The diseases from which differentiation may present certain difficulties are bronzed diabetes, pthiriatic melanodermia, some pituitary conditions with pigmentation, and conditions of pigmentation due to prolonged use of silver and acids. One of the chief difficulties lies in excluding racial pigmentation, and for that reason diagnosis of Addison's disease is very difficult in the tropics.

In doubtful cases certain authors have proposed the salt restriction test, which in real Addison accentuates the symptoms. In my opinion this is a dangerous test and should not be used. A parallel procedure would be to allow a diabetic to go into coma in order to verify the diagnosis.

Addison's disease, whether primary or cerebro-pituitary, should be differentiated from the adrenocortin deficiencies occurring in Simmonds' disease.

Therapeutics.

Rest, physical and mental, psychotherapy. The first thing to be done with an Addisonian is to place him at mental and physical rest. This often calls for great skill in appreciation of constitutional reactions. Directions must be individual. In severe cases rest should be absolute, the patient lying flat in bed as raising the head may cause vertigo. In milder cases activity can be permitted but with frequent intervals for rest in the recumbent position. All forms of physical exertion should be discouraged, as it has been observed that patients improving on cortin treatment have relapsed suddenly after return to work or a train journey. Detailed instructions should be given in writing. Mental rest is as important as physical, and can be induced only by physicians of keen psychological insight. It should not be forgotten that the fees of physician and nursing-home often overshadow most other worries, and thus tact and kindness in such matters should be shown.

Diet adequate in calories, vitamins, salt and fluid, low in potassium. Dietotherapy is of great importance in Addison's disease. It is not easy to feed the Addisonian because of the anorexia, nausea, vomiting and other digestive disturbances. Breakfast is a particularly trying meal as at that time nausea is pronounced. Nausea and vomiting must be palliated first. Cortin treatment contributes to this end, but in some cases temporary abstention from food is helpful, the patient taking iced drinks, brandy, whisky, champagne and a saline-glucose solution intravenously. Hydrochloric acid and tincture of nux vomica are good adjuvants, especially for anorexia.

The caloric intake is based mainly on carbohydrate foods, which also palliate the Addisonian hypoglycæmia. Meat should not be given in great quantity because of its possible toxic effects and because nitrogen metabolism is disturbed in this disease. Vitamins and salt should supplement the diet. Fluid intake should be supervised, especially as in spite of their dehydration these patients are not thirsty. If possible, 1,500 c.c. should be given in the form of fruit juices. Alcohol is useful for maintaining the caloric balance. Coffee and tea are allowed only in moderation, as they stimulate the sympathetic and draw too much upon the already exhausted adrenals.

The importance of avoiding foods rich in potassium has been pointed out by Wilder and his associates, and Sister Mary Victor has carefully outlined the technique of this type of diet.

In practice certain foods rich in potassium must be banned, such as soups, broths and gravies containing meat stock or meat extract, catsup, chili sauces, mustard and meat sauces and seasonings, dried fruit and vegetables, bran, molasses, chocolate. For the same reason bread, cereals, sugar and milk should be limited to the more highly refined products, the deficiency of vitamins resulting from this procedure being made good by administration of pure vitamins. The potassium content of meat and vegetables can be diminished by a certain method of cooking. According to Rynearson, vegetables should be cut into small pieces and cooked in 6–8 times their own bulk of water, all the water being thrown away. Meat should be cut into small pieces and cooked in a " parchment " paper bag in 6–8 times its bulk of water, which is thrown away. This procedure reduces potassium to one-quarter of the original quantity while other nutrients and extractives that give flavour are retained in the meat. Potassium should not be restricted in cases treated with desoxycorticosterone acetate, as in such cases drastic impoverishment in potassium may cause accidents including sudden death.

Salt and vitamin C. Both these can be considered as medicines. Salt can be given orally in 1-gram (enteric-coated) tablets, two or three being taken immediately after food or fluid until 10 or more grams have been taken during the day. If there is digestive intolerance normal saline can be injected. Severe renal lesions contra-indicate these procedures. The good results of sea-water preparations (Quinton) given orally in certain " asthenic " conditions occur because these conditions are mild cerebro-pituitary hypocortinisms. Salt should not be restricted in cases treated with desoxycorticosterone acetate.

Vitamin C is in my opinion an equally valuable medicine. There is probably a synergy between vitamin C and the adrenocortical hormone. It improves pigmentation and the general condition. Boerhaave's *simplex sigillum veri* should always be remembered, and simple medicines are often more useful than violent and complicated procedures.

Endocrinotherapy. This is composed of administration of adrenal cortical extracts, desoxycorticosterone acetate, and adrenal transplants.

Adrenal cortex extracts are the essential therapeutic agents. They are made according to the method of Swingle and Pfiffner. There are some excellent preparations on the market for general use. On general lines 50–100 c.c. are injected daily intravenously in severe cases, 20 c.c. intramuscularly in cases of moderate severity, 5–10 c.c. daily or on alternate days in mild cases. It is better to give the desired total quantity in divided doses than as one massive dose. Intravenous injections may cause accidents through protein impurities. The immediate results of this method are excellent, asthenia, digestive disturbances diminishing and disappearing, pigmentation also diminishing in some cases although this may be due not to disappearance of the pigment but to the increased hydration of the tissues. Adrenal crises are tided over, and patients often recuperate sufficiently to lead a nearly normal life. The remote results are not very brilliant. Adrenocortical extracts have added greatly to the comfort of the patient but little to his life expectation except for mild cases. This is because preparations are not yet potent enough, and also probably because in the adrenals the principle essential to life is not similar to the principle controlling blood chemistry, of which adrenocortical extract (cortin) is nearly exclusively composed. It is a fact that many Addisonians treated with cortin fail to improve although their blood chemistry may return to normal. It should be added also that Addisonians often have tuberculosis of the adrenals and other parts of the body which does not respond notably to cortin.

At all events, cortin does not give rise to serious side effects. Gynecomastia has been noted following its administration, but this complication cannot be ranked as serious.

Oral preparations of adrenocortical extract have one-tenth of the activity of the subcutaneous preparations, and as the latter themselves are not very active it is obvious that at present oral treatment has no place in the therapy of Addison's disease.

Desoxycorticosterone acetate is the second best. Its value lies in its cheapness. It is inferior to adrenocortical extract because it fails to correct hypoglycæmia and, usually, asthenia. It is more dangerous, and its administration should be carefully supervised. It is given intramuscularly in 5–10 and even 20 mg. doses. Precautions to be taken are (*a*) to avoid giving much salt at the same time; (*b*) to avoid withdrawal of potassium; (*c*) to watch for hypoglycæmia, which desoxycorticosterone cannot correct; (*d*) to restrict the activity of Addisonians undergoing this treatment, because desoxycorticosterone greatly increases the blood volume and raises the blood pressure, and physical

activity may therefore place an intolerable load on the circulation and cause cardiac insufficiency; (*e*) to watch for œdema, the first sign of overdosage. By taking all these precautions good results can be obtained.

Accidents from desoxycorticosterone acetate are due to two factors, the intense sodium chloride retention and potassium impoverishment. The sodium chloride retention causes subcutaneous œdema, pulmonary œdema, hypertension and cardiac insufficiency. Excessive potassium loss gives rise to certain asthenic and paralytic phenomena, and perhaps to certain sudden cardiac deaths observed in the course of this treatment.

There are great variations in the Addisonian response to desoxycorticosterone esters. Many cannot tolerate doses that may be innocuous to others. It is important to bear this fact in mind, although it is not possible to know beforehand the patient's degree of tolerance.

Administration of desoxycorticosterone acetate by pellet implantation is not, in my opinion, advisable on account of the risks of overdosage already discussed. The future will show whether the careful technique, including very exact observation with numerous tests, described by Thorn and Fizon, can obviate these risks. At present the less blind method of intramuscular injections is better, as this very valuable drug is a double-edged sword.

Adrenal cortex transplantation has given some very good results, and in view of the prognosis of Addison's disease and the frequent failure of cortin it should be considered. The technique has improved considerably of late. Since the adrenal medulla has been demonstrated to cause necrosis and suppuration the procedure is limited to the cortex. Homotransplants and heterotransplants have been used, but as good homotransplants are difficult to secure the use of animal adrenals seems the better procedure. Auslender reported fourteen cases showing good effects from heterotransplants, the longest case being observed for one year and eight months. Beer and Oppenheimer, who in 1934 were the first to transplant the adrenal cortex alone, suggest the combined use of adrenal cortical transplantation and Collip's adrenotropic fraction of the anterior pituitary to stimulate the transplant and any healthy adrenal rests the host may possess.

Testosterone is a good adjuvant. Thyroid is contraindicated as it may precipitate a crisis.

Adjuvant factors. Of minor medicines and physical agents tincture of nux vomica (10 drops before meals) is useful for anorexia. Hydrochloric acid (15 drops after meals) is effective in some cases with dyspeptic symptoms. Tonics should not be given as they tax the overburdened adrenals. Sedatives are more important because sleeplessness must be relieved. It is best to start with a biological sedative such as cratægus tincture (30–50 drops) and only in absolute necessity to resort to barbiturates, which in fact are toxic for the adrenals. Cysteine, proposed by Rivoire on the basis of the sulphur metabolic disturbances in Addison's disease, has not been studied to any extent. Adrenalin possesses only a historical interest.

Certain physical methods are indicated in mild cases. Open-air baths and

static electrical baths have given me the best results. Heliotherapy and ultra-violet irradiation are useless and even dangerous. I have noted severe aggravation in women with mild hypoadrenalisms (mild cerebro-pituitary form) after sun-bathing in the South of France. X-rays in so-called stimulating doses should not be prescribed, for as the stimulating effect of a dose depends on the reactions of the patient and not on the strength of the application itself we cannot know which doses are stimulating.

Treatment of the Addisonian crisis. In severe cases the following procedure may be used.

First day. Immediately (*a*) intravenous infusion of 1,000 c.c. of glucose saline to which 25 c.c. of adrenocortical extract may be added; (*b*) adrenalin, ½ mg., if pressure falls below 70 mm.; (*c*) subcutaneous injection of 25 c.c. of adreno-cortical extract. The procedure is repeated after 8–12 hours.

Second day. (*a*) Injection of adrenocortical extract, 5–10 c.c. every 4–6 hours; (*b*) one single injection of 15 mg. of desoxycorticosterone acetate; (*c*) intravenous glucose saline as on the first day; (*d*) frequent small feeds of milk, ginger ale, fruit juices.

Third day. Two injections of adrenocortical extract, 10–20 c.c., one of desoxycorticosterone acetate, 10 mg.

Fourth day. The general treatment outlined above begins.

Operations are very dangerous to Addisonians. On the eve and even just before the operation, cortin or desoxycorticosterone acetate should be administered.

CHAPTER XXXIX

ADRENAL PAROXYSMAL HYPERTENSION AND ADRENOVASCULAR SYNDROME

Paroxysmal hypertension is a disease characterised by adrenalin hypersecretion originating in an adrenomedullary, or in general in a chromaffin cell tumour, a phæochromocytoma. It is thus a primary adrenomedullary hyperadrenalinism. The first case was described by Labbé, Tinel and Doumer in 1922.

The neoplasm of the chromaffin cells of the adrenal medulla that determines paroxysmal hypertension may occur in the adrenal medulla itself, in the retroperitoneal paraganglions or in the carotid bodies. They are the only tumours proved to give rise to the typical clinical syndrome. No crises have been noted in patients with neoplasms of the primary neuroblastic cells, precursors of the sympathetic ganglionic cells of the adrenal medulla.

The medullary phæochromocytomas are usually unilateral and very rarely bilateral. They are sometimes associated with neuro-fibromatosis of the skin. Their volume varies, and they may reach a weight of 1,000 grams, but the majority are small, measuring 5–10 cm. in diameter. They consist of large epithelial-like polygonal cells whose cytoplasm contains granules giving both the chromate and iron chloride reaction of the adrenomedullary chromaffin

cell. The tumour contains adrenalin in very large amounts. A normal adrenal gland contains 0·23–0·9 mg. of adrenalin per gram of fresh tissue. Thrree, four and more milligrams per gram of fresh tissue are found in phæochromocytomas and as the tumour is often larger than the normal gland the quantity of adrenalin can reach enormous proportions. Belt and Powell's specimen contained 2 grams.

The attack of paroxysmal hypertension is due to sudden discharge of a large quantity of adrenalin, which causes hypertension by constricting the peripheral arterioles. By direct action on the heart the adrenalin causes palpitations, and by action on the respiratory nervous terminations causes dyspnœa and dilatation of the bronchi. It causes dilation of the pupils, inhibition of intestinal movements, hyperglycæmia and glycosuria. All these disturbances, reacting on the cerebral psychoassociational cortex, provoke intense anxiety.

The paroxysmal rhythm of adrenalin hypersecretion has not been explained. It is probable that nervous influences intervene.

The disease seems rare, and to date slightly over 85 cases have been described. However, this gives no precise idea of its incidence, for attention was drawn to the condition only a few years ago and thus many cases have passed and are passing unrecognised, and in addition the formes frustes have not been taken into consideration. It is equally distributed among men and women. It is found predominantly in the middle decades of life, the thirties, forties and fifties, but a case has been described in a child of two-and-a-half and another in a man of eighty-two.

The Major Form. The disease is characterised by paroxysmal attacks and a chronic condition supervening after a certain number of attacks or occurring in individuals who do not experience distinct attacks.

The paroxysm consists in a sudden attack of pallor, sense of constriction with anxiety, palpitations, headache, tingling and numbness of the extremities and elevation of the systolic blood pressure. Abruptly, often without any exciting cause, but frequently after an emotional upset, the patient becomes pale (although later he flushes and perspires). He feels the chest and even the abdomen constrict, with anxiety and palpitations which may overshadow all other symptoms. He breathes with difficulty and may expectorate froth as in pulmonary œdema. Hands and feet tingle or become numb. Vomiting may supervene and relieve the epigastric discomfort. He is giddy, the vision is blurred, he sweats and trembles. His head aches and feels full to bursting point.

If the blood pressure is taken during the attack the systolic pressure is revealed as very elevated, reaching 200–300 mm. The diastolic pressure, contrary to its movement in permanent hyperpiesia, is not raised in parallel. The pulse is either accelerated or retarded and the left ventricle dilated.

Hyperglycæmia and glycosuria may be encountered. A substance giving the pharmacological reaction of adrenalin has been found in the blood by Beer, King and Prinzpetal.

The whole attack lasts from thirty seconds to three hours. The end is as

sudden as the onset and leaves the patient exhausted. Death may occur during the attack from acute dilatation of the heart, cerebral hæmorrhage or an inexplicable cause.

The attacks come irregularly in the course of good health, but in some cases, as reported by Bauer and Leriche, happen at the same hour every day. They may occur spontaneously or after exertion or emotion. They may occur even at night, the emotional content of the dream probably being the exciting cause.

At first they are rare, but progressively increase in frequency as well as severity, and may happen several times in the twenty-four hours.

Interparoxysmal phase. In the intervals between attacks pressure is normal in the beginning, but sometimes a chronic hyperpiesia develops (Laubry, Thorn, McCullagh and Engel). Laubry described such a case in a patient who ultimately died of nephritis. Sclerosis of the vessels also develops even in young subjects (Kramer) and may be widespread.

Glycosuria may persist, and in fact in diabetes phæochromocytoma has to be considered (Duncan). The basal metabolism was permanently elevated in a patient of McCullagh and Engel. Adrenalin in the blood was thirty times the normal amount in the case of Stronbeck and Hedberg in the intervals of paroxysms.

An adrenal tumour may be palpated in some exceptional cases. Usually, however, it can be detected only radiologically after insufflation of the peritoneum. Intravenous pyelography, the first procedure to be applied, may help.

A patient of Neff had, besides the paroxysmal hypertension, manifestations of virilism which retroceded a few weeks after removal of a 96 gram phæochromocytoma. There was neither gross nor microscopic evidence of involvement of the adrenal cortex. This case remains inexplicable.

Course. The disease shortens life. Death may occur during the attack, as already indicated, from dilatation of the heart or cerebral hæmorrhage. An Addisonian terminal syndrome is noted in some cases. Such patients are extremely sensitive to operations and die suddenly even after a minor intervention. Any sudden death in the course of this disease may be due to ventricular fibrillation or to pulmonary œdema, and is thus comparable to death in experimental adrenalin poisoning.

Surgical excision of the tumour is the only treatment. The great difficulty lies in locating the tumour. If it cannot be found in the adrenal glands the accessory chromaffin tissue organs, the paraganglia, should be investigated in the region of the solar plexus or alongside the vertebral column. The tumour is difficult to recognise also because it may be so small as to resemble a lymph node.

Recovery after removal of the tumour is rapid and complete. According to Goldzieher, however, only the vascular changes, if they have occurred, do not retrocede.

Formes Frustes. These occur usually in the first stages of the disease but may be the sole manifestations of phæochromocytoma. They are attacks of

dizziness, headache, palpitations, often of nausea and vomiting. They are taken for " nervous attacks." In a case of Biskind, studied psychologically by Kasanin, a female patient shown later to have a phæochromocytoma noticed simply that when a man approached her with pleasure she suddenly started breathing heavily and felt palpitations of the heart, appearing outwardly greatly aroused although she felt but little. It embarrassed her to appear so emotional in situations of more or less casual nature. She felt without reason on these occasions an inner thrill, an inner excitement like a fright or shock. She was so deeply embarrassed by such reactions that she stopped seeing men. After operation she never experienced such attacks when in the same situation.

It is important to remember these formes frustes and take the blood pressure. Diagnosis is important, for in undiagnosed cases death may be the outcome of the attack. Further, as such patients are very sensitive to surgical intervention, even a minor surgical operation may end tragically if this disease exists unrecognised in them. Diagnosis of the formes frustes is difficult, and for this reason the internist should never be satisfied with the diagnosis " nervousness " or " hysteria." The blood pressure should be more generally taken during various attacks. The rarity of the condition, which after all may be only apparent, is not a justification for neglect. Clinical and radiological investigation for signs of tumour is an important element of diagnosis.

The Adrenovascular Syndrome. Progress in physiopathology reveals an endocrine-metabolic basis in an increasing number of chronic diseases An adrenomedullary or hyperadrenalinic basis is considered by some authors to exist in some cases of hyperpiesia, atherosclerosis and neurocirculatory asthenia.

Goldzieher accepts hyperadrenalinism as the physiopathological basis, or at all events as an important physiopathological factor, in many cases of hyperpiesia, and thus the existence of a hyperadrenalinic hyperpiesia. This conception is based on the medullary hyperplasia found in some cases of this disease and on the small nodules of phæochrome tissue similar to those produced by chronic nicotine poisoning (Staemler) and differing only in size from those found in paroxysmal hypertension and occasionally in chronic hypertension (Neusser and Wiesel, Laubry and Bernal, Reichardt). Other arguments in favour of the existence of a hyperadrenalinic form of hyperpiesia consist in the occurrence of hyperglycæmia in that disease (constant, according to Carrière) pointing to a probable hyperadrenalinic factor, and also the good effects of adrenal denervation in hyperpiesia (Galata, de Courcy, Crile). Clinically, there is no doubt that many hyperpiesias result from excessive sympathetic tonus. The adrenalin system is an extension of the sympathetic and its contribution to the genesis of hyperpiesia is thus very probable.

An adrenocortical contribution to the genesis of hyperpiesia also is evident. Hypercortinism, both cerebro-pituitary and primary adrenal, causes high blood pressure. Vaquez has found adrenocortical nodules in chronic hyperpiesics but the problem is not solved.

An adrenal element exists in the genesis of atherosclerosis. In 1918 and

subsequently I pointed out the general metabolic basis of atherosclerosis and connected this disease with cholesterol metabolic disturbances and thus with the regulators of cholesterol metabolism, which include the adrenals, principally the cortex. The adrenal element has since then been more distinctly demonstrated by Oppel and by Leriche. Hypercholesterinæmia is frequently found in atherosclerosis. Adrenalectomy improves atherosclerotic conditions (Oppel, Leriche). Adrenal grafts in rabbits (Leriche and Fontaine) provoked spasmodic phenomena followed by lesions of endarteritis obliterans, one of the most important atherosclerotic manifestations.

An adrenal element, hypo-adrenalinism, is regarded by Crile as the basis of many cases of neurocirculatory asthenia.

DISEASES OF THE PITUITARY-PINEAL GROUP

CHAPTER XL

ACROMEGALY

Acromegaly is characterised by a special enlargement of head and extremities and physiopathologically, predominantly, by hyperfunction of the phyone system. The symptom complex was described by Pierre Marie in 1886. Its connection with a pituitary disturbance was pointed out one year later by Minkowski, and its more precise connection with eosinophile hyperfunction and growth hormone hypersecretion has been the progressive result of the research of Massalongo (1892), Benda (1900), Dean Lewis (1905), P. E. Smith, and finally Cushing and Teel (1921).

Physiopathology and Etiology. The basic physiopathological disturbance is hyperfunction of the phyone system, *i.e.*, either hypersecretion of phyone or excessive reactivity of the cells and tissues of the body to phyone.

The hyperphyonism may originate in the pituitary centre of the phyone system (a phyone-hypersecreting eosinophile adenoma) and thus give rise to a pituitary acromegaly, or in the diencephalic centre of that system and thus give rise to a cerebro-pituitary acromegaly. In cerebro-pituitary acromegaly the intensive diencephalic drive on the antepituitary may manifest itself by eosinophile hyperplasia. In pituitary acromegaly the pituitary lesion is the hypersecreting tumour itself.

Hyperphyonism is also the basic physiopathological disturbance in another constitutional disease, pituitary gigantism. Brissaud explained the fact that the same pituitary disturbance could give rise to either acromegaly or gigantism by maintaining that in acromegaly the pituitary disturbance (hyperphyonism) occurred after epiphyseal union and thus could affect only the short bones of the extremities and those of the skull, whereas in gigantism the

hyperphyonism started before epiphyseal union and thus could involve the long bones. This view, however, has been proved inadequate, because acromegaly has been described also in children and reproduced experimentally in young animals. We are thus forced to accept a special reactivity of the tissues and cells of the individual patient to growth hormone, which directs the process towards acromegaly or to gigantism.

Besides phyone hyperfunction other neuro-hormonal systems are disturbed in acromegaly. The diabetogenin, adrenocortin, thyroxin and sometimes the mammogenin systems also are in hyperfunction. These coincident hyperfunctions are due in pituitary cases to a coincident hypersecretion by the eosinophile adenoma of all these hormones, and in cerebro-pituitary cases to a coincident hypersthenic reaction of the diencephalic centres of these neuro-hormonal systems. In men, but only in cerebro-pituitary cases, the testosterone system also may be in hyperfunction at the onset through a coincident hypersthenic reaction of its diencephalic centre but depression soon sets in through the antagonistic action of the growth hormone. In women the œstrin system is depressed at onset because of the combined antagonistic actions on this system of phyone and adrenocortin (mainly cortigenitalin). In pituitary cases gonadal depression is the rule in both males and females on account of the pressure exerted by the eosinophile adenoma on the basophile, thus the gonadotropic, component of the antepituitary. The hypersecretion of the pituitary tropins explains the enlargement of thyroid, parathyroid, thymus and adrenals seen in acromegaly.

These hormonal disturbances determine great changes in the metabolic functions of the body. Energy metabolism is often increased, as shown by the increase in basal metabolism due to the hyperthyroxinic element. Protein anabolism is increased, being connected with the protein anabolic function of the growth hormone, and thus the nitrogen balance is positive. Creatinine is increased in the urine, probably in relation to increase of the muscular mass. Uric acid is excessive in the blood, through increased nuclear substance in the body, according to Falta. Carbohydrate metabolism is disturbed in the direction of hyperglycæmia and glycosuria, through coincident hypersecretion of diabetogenin. Water metabolism is disturbed by the pressure exerted on the postpituitary centre of antidiuretin by the eosinophile adenoma. Usually polyuria or diabetes insipidus is observed but oliguria has occurred in rarer cases.

As well as these general metabolic disturbances, and probably connected with them, local disturbances of the cellular metabolism occur resulting in excessive multiplication and enlargement of the cells connected with osteogenesis and of the cells of various organs. Acromegaly is not only a disease of the skeleton but is of the whole organism, and megalosplanchny is one of its important features.

Primary pituitary acromegaly is a relatively rare disease, occurring chiefly in adults, the highest incidence appearing in the third decade. It is due to an eosinophile adenoma of the antepituitary. These tumours may be small

and detected only on microscopic examination, but usually they are large, weighing 3–30 grams. Histologically they are composed of eosinophile cells and in some cases are cystic. They may be situated in the pituitary tissue remaining from embryological development in the craniopharyngeal canal, or in the pharyngeal pituitary.

Cerebro-pituitary acromegaly is more frequent, especially in its formes frustes. It is also a disease of the adult, although in some cases, usually associated with gigantism, it has been described in children. In rare cases it is caused by tumours of the hypothalamo-pituitary region (but not eosinophile adenomas) pressing on the hypothalamic centres of the phyone system, but usually it is determined like all cerebro-pituitary endocrinisms by an interplay of a genogenic factor of inferiority of the phyone system and of various environmental factors such as infections, trauma, mental factors and other endocrinopathies. Infections act through the mechanism of diencephalitis (an extension of a sinus infection has been accepted by some). Traumatic factors are exceptional but interesting, such as the case of Guillain and Sigwald, in which acromegaly started eight months after removal of a bullet from the occipital region, and that of Frank in which the disease began after removal of a piece of bone from the nose. Mental factors are accepted as possible by Kehrer. Among other endocrinopathies gonadal disturbances are prominent, the hyperphyonism in these cases representing an abnormal compensatory reaction of the phyone system. The temporary acromegalies of pregnancy, the acromegaly of some eunuchs and some mild juvenile gigantisms have this origin.

Symptomatology

Pituitary or Neoplastic Acromegaly. *The initial syndrome.* The disease starts slowly and progressively. In some cases the initial symptoms are of vaguely nervous nature, but this mode of onset is less distinct than in cerebro-pituitary cases.

In most cases the onset is marked by nervous pressure symptoms, hypogenital manifestations or morphological modifications. Headache, often very intense, nausea, vomiting, and more frequently failure of vision and paralysis of the oculomotor muscles, all due to the pressure exerted by the intrasellar tumour, are often the initial manifestations of acromegaly. In other patients the disease begins with hypogenital manifestations, principally diminution or stoppage of menstruation. Onset with morphological manifestations is rarer because less likely to be observed by the patient, but in some cases attention is drawn by an increase in the size of hands or feet shown by the need for larger gloves (noted by women) and larger shoes (noted by men), and the entourage has often been helpful.

The acromegalic habitus. This is composed of enlargement of head and extremities, cyphosis, and certain modifications of the skin. Stature varies but is often increased, indicating strong phyone function earlier in life.

The head, including the face, is not only unduly large, but also shows other peculiar features. The facial bones are well developed, the superciliary ridges

prominent. The forehead is wide, the nose long, large, voluminous, of "pulcinella" appearance. The eyes are disproportionately small, but are sometimes protruding and overhung by thick long eyebrows. The ears are voluminous and planted far back on account of the forward growth of the facial bones. The lower jaw protrudes distinctly and supports an unusually large tongue. The lips are thick and blunt. The whole appearance of the face is hexagonal and virile, even in women.

The hands and feet are abnormally large. The hands may be en longue, a feature common to acromegaly and gigantism, or en large, a feature more characteristic of acromegaly. In the latter case they are wide, with large wrists, short, thick and stubby fingers, often sausage-shaped through hypertrophy of the soft parts. They are "spade hands." The nails are larger than normal but because buried in the surrounding hypertrophic tissue they appear small. The lines of the hand are accentuated and separated by abundant hypertrophic tissue, giving the entire extremity a padded appearance.

Cyphosis is seen in nearly three-quarters of cases, and when it coincides with a forward projection of the sternum a double Punch-like hump is formed. The spine is generally rigid, and its condition may shorten the stature. Usually cyphosis affects the upper dorsal, with compensatory lordosis of the lumbar region.

The skin modifications are hypertrophy, hypertrichosis and pigmentation. Hypertrophy occurs in the regions of election of the acromegalic manifestations, where the skin is thick and infiltrated, although less than in myxœdema. In some cases the skin shows furrows and folds going from forehead to the nape of the neck, and in the neck horizontally from ear to ear. This condition is known as cutis verteis gyrata. Hypertrichosis is of hypercorticogenital type, and is in fact due to hypersecretion of adrenotropin. It is a body hypertrichosis, localised principally on the distal extremities from elbow to fingers, from knee to sole, especially on the extensor surfaces. The scalp shows the contrary, hypotrichosis occurring in the form of alopecia beginning at the fronto-temporal line and developing along the temporal ridge until finally the entire vertex is bald. Pigmentation is frequent in the form of chloasma, vitiligo or irregular brownish freckles on exposed surfaces. It is probably linked with hypersecretion of intermedin.

The whole appearance in complete cases, with the facial deformities, the huge hands hanging from the bent back nearly to the knees, is gorilla-like. It is probable that anthropoid apes repeat in their normal development the particular hyperpituitarism which in humans occurs only pathologically.

Radiological investigation completes the details of these skeletal deformities. It shows the exaggerated development of the head and facial bones, abnormally large sinuses and mastoid cells, and the disproportionate enlargement of the sella turcia due to the causal tumour. In the hands it reveals the arrow-shaped tufting or mushrooming of the distal phalanges, the widening of the phalangeal and metacarpal bones, the overgrowth of tuberosities and enlargement of the carpal bones. The same features are seen in the feet.

The spine shows increased width and depth of the vertebral bodies, hypertrophy with osteophytic overgrowth causing bridging of the intervertebral spaces. In fact, a hypertrophic osteoarthritis is revealed. There is enlargement of the cancellous bone in general. This is the basic mechanism. Later, when hypofunction supervenes, there is secondary sclerosis with production of exostoses. Goitre with other manifestations of hyperthyroidism often complicates the picture. It is incorrect to describe such cases as associations of acromegaly with Graves' disease. The hyperthyroidism in these cases is part of the eosinophile hyperpituitarism.

Reactivity, sexual, mental and organ syndromes. Asthenia is often marked but is sometimes preceded by increased strength and activity. Excessive perspiration is very common, and due probably to hyperthyroidism. Infective processes of the sinus are frequent, showing the importance of the endocrine factor in treatment of sinusitis.

Hypogenitalism is the rule. In females hypomenorrhœa and amenorrhœa are always outstanding manifestations, often preceding the other symptoms and sometimes giving rise to errors of diagnosis. Sterility is constant. Men show loss of potency and of libido, and sterility. Exceptionally, in some cases of cerebral acromegaly hypersexualism is noted at onset, and is due to a coincident hypersthenic reaction of the diencephalic centre of the gonadal hormones. This hypersexuality, however, is always transient because of the predominant sex-inhibiting influence of growth hormone.

The psychological symptomatology is rich, based on hormonal factors, intracranial pressure (in neoplastic cases) but chiefly psychogenic factors, because few diseases inflict such severe psychical trauma as this terrible deformity. Loss of memory is constant, and cerebration as a whole is low in acromegaly. Depression due to psychogenic factors is nearly constant and is accompanied by insomnia. Attacks of somnolence, dreamy absorption and fugues have been noted. Psychoses develop in predisposed individuals. They are of depressive type. Hallucinations have been described by Villaret, and exhibitionism in a case of Picard.

Headache, hyperpiesia with cardiac insufficiency and varices, constipation and chronic arthritic manifestations are the outstanding organ manifestations. Headache exists also in non-neoplastic cases, and is attributed to the pituitary disturbance itself. It is usually paroxysmal, consisting in a full feeling and throbbing within the skull. It often takes the form of migraine. It coincides with excess of gonadotropin in the urine, is aggravated by antepituitary preparations and relieved by œstrin. Hyperpiesia is very frequent and due to coincident hypersecretion of adrenotropic hormone. Cardiac insufficiency is secondary to hyperpiesia, but the heart hypertrophy due to the action of the excessive growth hormone contributes. Many acromegalics die of heart conditions. Varices with their sequel thrombo-phlebitis are fairly common and show the special action of the pituitary on the veins. Constipation is usually due to megacolon or dolichocolon, a result of the basic hyperphyonism. Chronic arthritic manifestations are almost constant. Acromegalics complain

of pains in the joints, and radiographs show lesions of "hypertrophic arthritis." In fact, hyperphyonism is considered an important factor in the genesis of chronic hypertrophic arthritis (osteoarthritis) in general.

Tumoral and biochemical syndromes. In the frequent neoplastic cases, symptoms of intracranial pressure coincide and may even dominate clinically. They consist in ocular disturbances, manifestations of general cranial hypertension and radiological signs. The ocular disturbances are mainly a heteronymous bilateral hemianopia, often preceded by changes in colour vision, and sometimes a central scotoma. Optic atrophy and choked disc are rare. The manifestations of cranial hypertension are chiefly intense headache, with projectile vomiting, differing from the purely hormonal headache so frequent in hyperpituitarisms. The radiological signs centre on the enlargement of the sella turcica.

Laboratory findings refer to the metabolic disturbances described in the physiopathology of this condition. Clinical importance attaches to the increase of basal metabolism and of the specific dynamic action of proteins, hyperglycæmia and glycosuria, and the increase of urinary creatinine. *B*-gonadotropin is found in excess in the urine, particularly in cases with headache. No satisfactory explanation has been given of this symptom.

The course of the disease shows exacerbations, waves of hyperpituitarism, and ameliorations amounting in some cases to remissions. These are more frequent in cerebro-pituitary than in primary pituitary acromegaly.

The usual duration is about eight years, but some cases have lasted only between three and four years, and others, probably more of cerebro-pituitary than primary pituitary form, have been prolonged to fifty years.

Death occurs through intercurrent infection, cerebral attacks, diabetic coma, cardiac insufficiency or cachexia due to hypopituitarism, which may succeed hyperpituitarism.

Cerebro-pituitary Acromegaly. In its complete form, which usually is accompanied by eosinophile hyperplasia resulting from the hyperfunction due to the diencephalic drive, non-neoplastic acromegaly shows the same symptoms as those described for neoplastic cases, except for the tumoral symptoms. The onset, however, is often marked by various nervous symptoms, described by Marks in his auto-observation (Marks was found at autopsy to have a non-neoplastic acromegaly). This physician noted in himself at onset malaise, pronounced fatigue, desire to keep still, inability to work, intolerance of noise and bright light, giddiness, a feeling of very severe illness, painful muscular cramps, wandering pains as in tabes with a particularly persistent pain in the zygomatic arcade. The duration of these cases is longer than that of neoplastic forms.

Formes frustes of acromegaly, however, are the usual manifestations of non-neoplastic acromegaly. These forms are seen frequently by clinicians with an eye for the human form. The most important are the transitory acromegalies of pregnancy, the acromegaloid biotype, and the "sinusitis" form.

The acromegaloid biotype is, as the term implies, more a constitutional type than a disease. There are individuals born with a tendency to hyperactivity of their phyone system. They are tall. Head, hands and feet are large. The face is hard, often with spaced teeth, powerful jaws, large nose, projecting chin, strong muscularity and sexuality. They are physically active, often of fighting disposition, and frequently active also in the mental sphere. According to some authors, such persons are predisposed to develop a real and complete acromegaly. A depressive condition with obesity develops later from hypofunction succeeding hyperfunction of the antepituitary.

The transitory acromegaly of pregnancy develops in women of this acromegaloid biotype. Erdheim has noted a constant enlargement of the pituitary during pregnancy. Such women show subdermal infiltration about the short and flat bones of face and extremities, and blunting of peaked bones. Hands and feet seem to enlarge. The face assumes a hard, virile expression. Hair grows abundantly on the arms and face. Chloasma is intensified. As a rule these symptoms disappear after delivery, but in one case reported by Engelbach symptoms continued until a classical acromegaly was established.

The " sinusitis " form is characterised by frequent infection of the sinuses, and frequent allergic manifestations in the sinuses, occurring in individuals of acromegaloid biotype with particularly full development of the sinuses. Such patients are seen principally by otorhinolaryngologists, but the constitutional basis of the condition is distinct.

Therapeutics

In mild forms of neoplastic acromegaly, and particularly when there are no serious visual disturbances or other symptoms of intracranial pressure, general constitutional methods, endocrinotherapy and radiotherapy are used. General constitutional medication is important, its principal elements being psychotherapy to help the patient to bear his tragic deformity, regulation of diet and hygiene, and sedatives. Endocrinotherapy is not very effective, but œstrogens can be given to women. Radiotherapy has many chances of success, eosinophile tumours responding better to this method than chromophobe adenomas but less notably than basophile adenomas. Dosage is delicate because high dosage may determine various disturbances, and in particular may hasten the passage of hyperpituitarism to hypopituitarism. Thus endocrinological following up is necessary for acromegalics undergoing this treatment.

In severe forms, especially when radiotherapy has failed and vision is threatened, hypophysectomy is indicated. It is an operation with high mortality (10 per cent. usually, 2·4 per cent. in Cushing's figures). Improvement is recorded in 50–60 per cent. of cases. Palliative surgery is indicated in some cases for improvement of the process of biting. Special dentures are made, or a piece of bone is removed from each side of the lower jaw.

In non-neoplastic acromegaly the internistic general constitutional treatment already described is the basic therapeutic procedure. Œstrogenic treatment often gives very good results in women, far better than in neoplastic

cases. Radiotherapy can be tried but is less effective than in neoplastic cases and the danger of hypopituitarism is far greater. Special palliative surgery is indicated in severe cases.

CHAPTER XLI

PITUITARY GIGANTISM

Sir Arthur Keith put his finger into the skull of the giant Charles Byrne and recognised this physiopathological form of gigantism. In 1892, Massalongo worked out the relation between acromegaly and gigantism, and thus developed the conception of pituitary gigantism, suggesting that acromegaly was merely a gigantism occurring after the closure of the epiphyses. His work was amplified by Brissaud and Meige and Launois and Roy. In 1921, Evans and Long produced gigantism by injections of antepituitary extract.

Hyperfunction of the phyone system, hyperfunction of growth hormone, occurring before the end of the period of growth, *i.e.*, before union of the epiphyses, is the primary physiopathological event in this disease. The excessive phyone acts on the diaphyso-epiphyseal cartilages and stimulates osteogenesis, *i.e.*, growth of the long bones. It also acts, however, on the periosteal osteogenesis of the small bones and causes a more or less distinct acromegalic picture. Many "pituitary giants" are acromegaloid. Certain racial and familial macrosomias may be due to a genogenic abnormal hyperfunction of the phyone system.

The gonadal systems (testosterone or œstrin) are involved secondarily, being depressed by the hyperfunction of growth hormone which is antagonistic to these systems. In some cases, however, exclusively of cerebral hyperphyonic macrosomia, there coincides a hypersthenic reaction of the diencephalic centre of the gonadal system and thus hypergenitalism, which, however, can be only transitory.

As for acromegaly, a neoplastic or purely pituitary and a non-neoplastic or cerebro-pituitary hyperphyonism are described as factors of macrosomia or gigantism. Neoplastic hyperphyonism originates in an eosinophile adenoma and is exceptional. Cerebro-pituitary hyperphyonism results from the action of various environmental factors on a genogenically labile phyone system. Infective factors (encephalitis) are the only distinctly known causes, and are demonstrated by the cases in which intensive growth occurs in children after infectious diseases. Genetic factors of special cellular sensitivity to growth hormone intervene.

The Common Form. The accentuated form of hyperphyonic macrosomia, the gigantic form, can serve as model for the clinical description. The disease begins at an early age. The essential feature is acceleration of physical development, which at onset can usually be detected only by clinical anthropometry. At four or five years of age the child is as tall as a nine- or ten-year-

old. The development of sexual organs and characters is usually normal.

When the disease is fully established the exaggeration of height dominates. Small giants reach a height of 6 feet 6 inches, and medium giants range between this height and 6 feet 10 inches, and the largest giants show any figure above 6 feet 10 inches. Such heights are exceptional, but Charles Byrne, who was dissected by John Hunter and whose skeleton is in the Museum of the Royal College of Surgeons, was 8 feet 10 inches tall, and the Russian Muchnow, on exhibition in London in 1905, reached a height of 9 feet 3 inches.

Pituitary giants are macroskelic, and thus the span is greater than the height and the lower segment larger than the upper. In these giants growth hormone acts intensively until the closure of the epiphyses, which occurs at the normal time when gonadotropic secretion remains normal, or belatedly when gonadotropic hormone secretion is deficient.

Acromegalic features are constant although varying in degree. Even when there is no great enlargement of the head the face appears hexagonal as in acromegaly, the lower jaw protrudes, the teeth are spaced, the traits of the face are blunt, hands and feet large but long. Cyphosis is nearly constant. The external genitals, at all events at onset, are well developed. When the acromegalic features are pronounced the patient is termed an acromegalic giant, but in fact all hyperphyonic or pituitary giants are more or less acromegaloid.

Sexually hypogenitalism dominates, in both men and women. There occurs, however, particularly in men, a phase of hypergenitalism which may last for some time but is always succeeded by a hypogenitalism of exhaustion. This initial hypergenitalism results from concomitant hypersecretion of gonadotropin. In some mild hyperphyonic giants sexual functions may approach normality.

The reactivity characteristics develop in two phases. At onset there may be intense muscular hypersthenia (Carnera type), due probably to hypersecretion of adrenotropin. This may last for years but in invariably followed by muscular asthenia. In some cases muscular asthenia exists from onset. Coinciding with the muscular hypersthenic phase increased appetite is noted, and may reach enormous proportions. Thus, a giant observed by Humbard habitually consumed 6,000–8,000 calories per diem. This symptom also is not permanent.

The mental condition looms large in the clinical picture. Cerebration is defective except in mild cases, and deteriorates with the years. Few real pituitary giants have sufficient mental capacity to maintain their independence after thirty. Behaviour disturbances are constant, and are due to psychogenic factors. These individuals are conscious of their handicap. They react by inattentiveness, apathy, antagonism and surliness. They become prone to fantasy thinking, seeking through their day dreams to escape from their feeling of inferiority. In a more intense form of compensation they develop a craving for the limelight. As they cannot achieve their object with

their social equals they seek it with their inferiors. They commit foolish acts merely to obtain attention. They may lie, steal and perpetrate pointless offences. Psychoses develop in predisposed individuals on the basis of their antisocial reactions. In two giants of moderate degree I have observed the development of a manic depressive psychosis. Here also the interaction of hormonal and psychogenic factors enters into consideration.

All organs are enlarged in proportion. Radiologically remarkable enlargement of the sinuses of the face is detected. The sella turcica is enlarged, not always as the result of a tumour but in relation to the over-development of the skeleton. In the rare cases of gigantism due to an eosinophile adenoma of the antepituitary the usual intracranial tumoral symptoms occur. Laboratory findings refer to the metabolic disturbances existing in these giants and similar to those seen in acromegaly. Basal metabolism is increased.

There are two distinct phases in the history of hyperphyonic giants, especially in those of cerebral origin, a phase of hypersthenia with high muscular tone and often with hypergenitalism, and one of hyposthenia with depression of musculature and sexual power. On the whole the life of pituitary giants is short, and death from tuberculosis is frequent. Psychoses and imbecility are common.

Formes Frustes and Localised Forms. Formes frustes are often encountered. They consist in slight deviations from the maximum normal height. They are usually genogenic, *i.e.,* due to a gene which acts through the antepituitary, and are thus often racial and familial like the deep constitutional macrosomias.

Localised gigantisms are interesting as indicating a special reactivity of the body to the growth hormone. The most frequent of these forms are those involving one half of the body. Some cases of megacolon can be considered as localised visceral gigantism.

Therapeutics. The best method is administration of strong doses of testosterone for the male, œstrin for the female. Results are far from perfect but early treatment checks excessive growth to some extent in mild cases. Testosterone administration must be supervised strictly, as in some cases it accelerates growth. Pineal gland also has been administered in such cases, but with indefinite results. Radiotherapy can be employed but with careful endocrinological supervision, because this method depresses gonadotropic function.

Differerntial Diagnosis.

Hypogonadal or Eunuchoid Macrosomia. This is a eunuchoidism of macrosomic form. The primary physiopathological disturbance is not hyperphyonism as in the preceding form, but hypogonadism. Hyperphyonism is secondary, growth hormone hyperfunction occurring because of the deficiency of its antagonistic gonadal hormone, testosterone or œstrin. To this essential difference in physiopathology corresponds a difference in clinical features and therapeutic handling.

Such cases show the tallness and macroskelia of hyperphyonic macrosomia, but the tallness does not reach the high figures of the latter while the macroskelia is more accentuated. Hypogonadism, often with cryptorchidism, dominates the clinical picture.

Hypogonadal gigantism can be checked by testosterone, œstrin and gonadotropins. As these sexual hormones can accelerate growth, however, they must be used with care. Radiotherapy of the pituitary could be tried, but with careful supervision, because although some radiologists regard certain pituitary radiotherapy as stimulating the question is still very obscure.

The term eunuchoid gigantism, by which some authors denote all gigantisms with macroskelia (the so-called eunuchoid proportions), is confusing. Macroskelia exists in pituitary as well as in hypogonadal, or real eunuchoid, macrosomia, and clinical precision therefore demands that the term eunuchoid gigantism, which originated when the conception of macrosomia was vague, should be discarded.

Temporary Macrosomia of Pubertas Praecox. Pubertas præcox of adrenocortical, testicular or ovarian origin is characterised at onset by macrosomia. In fact, this disease, constituted at onset by acceleration of statural and genital development, is often designated as macrogenitosomia. The macrosomia of pubertas præcox depends on the growth properties of testosterone, certain adrenal steroids and of œstrin. It is only temporary because the early epephyseal union due to the hypergonadal component of the disease arrests statural growth, and when seen at a more advanced age these patients are microsomic instead of macrosomic. This form is mentioned here for differential diagnosis of the macrosomias of the young, but has been already described elsewhere.

Deep Constitutional Macrosomia. This is more a biotype than a disease. It is due to an abnormal gene which imposes a crescendo growth metabolism on all cells of the body, or acts on the various organisers of the segments of the body. In its mildest form it is often hereditary. Its etiology is that of gene heredity or gene mutation.

The presenting symptom is increase in stature, which, however, is not greatly above the higher limits of the normal and never reaches the gigantic proportions seen in hyperphyonic (pituitary) macrosomia. Body proportions are normal. There is not the macroskelia shown by hyperphyonic macrosomia. In mild cases, where the individual measures about 6 feet 3 inches, no other important symptoms are seen. In some more accentuated cases, however, psychological disturbances are apparent, these individuals, particularly women, being conscious of their dysplasia. Further, in these as in all persons who deviate from the "normal" habitus, resistance to disease is somewhat diminished. This is a general law. Bumpus examined the sparrows found dead after a storm, and observed that most of them belonged to extreme varieties of the species.

CHAPTER XLII

PITUITARY INFANTILISM

Infantilism denotes persistence into post-puberal ages of features belonging to the infant, *i.e.*, infantile stature, sexuality and mentality. In other words, infantilism consists in arrest or retardation of statural, sexual and mental development.

The term infantilism and description of the condition were first given by Lorain in 1871 in the preface to a thesis by his pupil Fanceau de la Cour. In 1902, Hastings Gilford described such cases as "ateiliosis." The work on which modern views of infantilism are based is that of Souques and Chauvet (1913).

Cerebro-pituitary, the most frequent form of infantilism, combines hyposthenia of the phyone, gonadal and thyroxin systems originating in the diencephalic centres of these systems and thus acting on their pituitary links. There is no primary pituitary infantilism, as a primary pituitary lesion cannot be so selective. This combined triple neuro-hormonal deficiency is determined by an interplay of genogenic inferiority of these systems and of such environmental factors as tumours pressing on the diencephalon (exceptional), encephalitic lesions localised in the diencephalon and, principally, nutritional factors (general malnutrition, digestive disturbances and hypovitaminoses).

Symptomatology. The Complete Form.

The developmental syndrome. This is a disease of post-natal development "from birth to maturity" of stature, gonadal functions, intellect, temperament. The developmental retardation can be followed by the parents and elicited from the history. The statural retardation is the most striking feature. When the disease begins in utero the new-born infant may already be tiny. In other cases growth is normal until a certain age, when after an infection or without apparent reason simple anthropometric measurements show the yearly increases to be below normal. Retardation in intellectual development, due to the addition of hypothyroxinism, is appreciated with greater difficulty. However, delay in speaking is often a striking symptom. Infants are expected to say "pa-pa" and ma-ma" at twelve months, to have a vocabulary of five or six words at eighteen months, and then to progress uniformly, given good environmental conditions. Later, at the kindergarten age, intellectual retardation is appreciated more distinctly. Gonadal retardation is noted later, at puberty.

The infantilistic triad, microsomia, hyposexualism, mental retardation with infantile mannerisms. The first abnormality to strike the beholder is the discrepancy between the apparent age and the calendar age. First glance may gather the age to be seven, whereas it is thirteen or fourteen. The adolescent has an infantile appearance.

1. Microsomia or dwarfism is the first element of the infantile triad.

Stature varies from slight deviations from the normal to pronounced dwarfism, without, however, reaching the Lilliputian proportions of deep constitutional dwarfism. The body segments are subnormal in size. Microskelia is encountered when hypophyonism predominates, macroskelia when the hypogonadal element is important. The skin is very thin. General thinness is the rule (the chétivisme of French authors) except when the thyroid element or a pituitary fat-metabolic element intervenes (fat infantiles). Axillary and pubic hair are poorly developed and may even be absent at an age when they should have developed. Facial expression may be lively, except if an accentuated hypothyroidean element gives an empty expression. The teeth show the hypogonadal stigma of large central incisors, small lateral incisors and blunt canines. There is a certain laxity of the ligaments. The external genitals are hypoplastic.

Radiological findings are interesting. The cranium is small but the face even smaller in relation to the brain case. A striking absence of diploë is seen, so that the inner and outer tables are in close approximation. As a result the vault of the cranium is thin, hard, dense and not vascular. The paranasal sinuses and the mastoid cells are very poorly pneumatised, the petrous pyramids dense and cancellous. The frontal sinuses are often absent. In early cases the cranial sutures are patent. Dentition can be delayed. The sella turcica is small with closely approximated clinoids, a feature bound up with the general diminution in the growth of the cranium. In the exceptional cases in which dwarfism is due to a tumour the sella turcica can be distended. The bones of the limbs show normal ossification centres but delay in the union of the epiphyses. The bones are small and fragile and the phalanges pointed.

2. Genital hypoplasia and hypofunction are manifested variously. In males, testes are often undescended, and when descended are often smaller than usual. External genitals are hypoplastic. Libido does not develop. There is a tendency to passive homosexuality, but this is more a manifestation of weakness of character than of feminised libido due to hypotestosteronism. In females, menses occur late, are irregular and are separated by long intervals. There is some degree of utero-ovarian hypoplasia.

3. Mental retardation combined with infantilistic behaviour traits completes the infantile triad, and is usually the reason for which parents bring these children to the physician. Except when the hypothyroxinic element is strong the mental retardation is not generally marked, but is simply a difficulty in keeping up with the class in school. It depends in great part on a certain nervousness, anxiety, emotivity and inferiority complex accentuated by the indifference of teachers towards retarded children, the mockery of schoolfellows and the over-anxiety of the parents, who to avoid such conflicts keep infantile children at home under private tuition. Infantilistic traits appear. The adolescent of fourteen has the character of a child of nine. He fails to show the drive, interest and competitive spirit in sports corresponding to his calendar age, but plays and daydreams like a small child. Infantile girls of sixteen play with dolls. Such traits are largely of hypogonadal origin, and

occur because the gonadal hormones have been insufficient to exert on the cerebral cortex the maturing influence that marks the passage from infancy to adolescence. Psychogenic factors acting on such endocrinologically unbalanced individuals cause behaviour disturbances which can even reach the level of psychoses. Puberty presents a series of great problems to the developing human being. To tackle them perfect neuro-endocrine balance is needed. When this balance is imperfect and when the patient feels that he is inadequate a series of psychological reactions is initiated. He withdraws into himself and thus becomes schizoid. He develops various mannerisms to push himself into the limelight. He becomes sad or irritable.

The details of the psychological features of infantilism vary with each individual patient. They depend on the relative proportions of hypogonadism and hypothyroidism. They depend too on environment, upbringing, mental reserves and mental reactivity, which is a feature of the genetic constitution.

Background symptoms. Asthenia is encountered as in most endocrinisms. The hypogonadal element in particular makes these boys averse to sports. The tendency to colds is often pronounced. It is due to the hypothyroidism but also to maldevelopment of the sinuses of the skull, due to hypophyonism. The voice of males does not break—a typical hypogonadal manifestation.

Laxity of the joints, another hypogonadal feature, is frequently seen. It combines with the muscular under-development and the asthenia due to the same factor to disturb the gait in children. Sufferers from cerebro-pituitary infantilism are often taken to the orthopædist for special treatment, but orthopædic appliances are usually of no avail, if not detrimental, when the basic neuro-endocrine disturbance is not corrected.

Basal metabolism is lowered in most cases, and depends on the hypothyroidean element. Other biochemical findings indicating this complicating endocrinism are seen, such as increase of cholesterol in the blood. Hormonal studies have not yet yielded definite results.

Course of the disease. In untreated cases life is shortened. Life flows at a low level, and such individuals are incapable of being useful members of the community. Death occurs early from intercurrent infections, these patients being very fragile vessels.

An interesting element in the evolution of some infantiles is the possibility of further growth even after the twenty-first year through non-union of the epiphyses.

Hence the importance of early recognition of the disease, for early treatment can prevent the patient from becoming a misfit or at all events can obviate a major handicap in life. Knowledge of the features of infantile development and of simple anthropometrical methods and mental tests are therefore necessary.

Special Forms.

Pituitary Dwarfism. This is a form of pituitary infantilism in which hypophyonism predominates. It is rare not to find in such cases a mild hypogonadal element (delay in the union of the epiphyses) and a hypothy-

roidean element (diminution of basal metabolism). Pure dwarfisms are not of pituitary origin.

Psychological Infantilism. In this form, well described by Anton, the psychological manifestations of infantilism predominate. Such patients maintain at an advanced age the psyche of the child. Their play is childish, they have childish logic, the childish tendency to imitation and daydreaming, and the anxiety and need for support of an early age. They associate with those younger or inferior, and have an infantile attachment to their mother. They are very sensitive to all impressions. They are not mentally retarded. Their memory, association of ideas and perception are normal, but their attention is easily distracted. They may be virtuosi in music, for example, but never creative. This psychological picture differs from that of the eunuchoid, and is clearly distinguished from mental deficiency with its disturbances in association of ideas and memory, its loquacity and perversions.

A careful clinical examination will detect other organic traits of pituitary infantilism.

Therapeutics.

Success depends on early diagnosis and on the early application of skilled treatment. Modern hormone treatment can transform a human being condemned to a wretched and inferior life into a useful and happy member of the community. This treatment, however, is often of difficult application because too long and delicate.

1. General constitutional methods are of primary importance. Psychotherapy is mainly educational and is rendered necessary by the mental disturbances shown in this disease. Correction of all hygienic and dietetic defects and provision of a complete and healthy diet rich in proteins and adequate in vitamins are important. The best physical methods are ultra-violet irradiation and certain climates, notably the stimulating resorts of the Isle of Thanet type.

2. Endocrinotherapy, the greatest of recent advances in the treatment of cerebropituitary infantilism, takes the form according to the indications of gonadotropic hormones, growth hormone, total anterior pituitary extract, thyroid and adrenal cortical preparations and embryonic extract in various combinations. Testosterone is useful for males and females for its anabolic effects. An exact programme of treatment, however, cannot be given as it is entirely governed by the individual reactions. Adjustment of growth hormone to gonadotropin is especially delicate because of their antagonism. On the whole, endocrinotherapy is a complex procedure which in skilled hands often yields remarkable results.

3. Treatment of the cryptorchidic form of pituitary infantilism has lately shown some unfortunate developments in research on treatment of "undescended testicle." Undescended testicle is not a disease but a symptom found in certain deep constitutional conditions, in some inflammatory conditions, in male cerebro-pituitary eunuchoidism, pituitary infantilism and pituitary adiposogenitalism. This enumeration alone shows how irrational are statistics of therapeutic results in "undescended testicle," under which

heading are grouped pell-mell very different conditions. The irrationality of these statistics becomes even more blatant when it is recognised that research bearing on only one disease, pituitary infantilism with cryptorchidism for instance, must take into account individual factors. There is no "treatment of undescended testicle" but treatment of various diseases with undescended testicle as one of their manifestations, and in these diseases individual features are of paramount importance.

When pituitary infantilism is accompanied by undescended testicle, or even when a case showing undescended testicle has been diagnosed as an oligosymptomatic form of pituitary infantilism, endocrinotherapy is directed by special indications apart from the individual features. The clinical observation of recent years has shown the basis of this treatment to be pregnancy urine gonadotropin, and a necessary supplement to take the form of anterior pituitary extract, thyroid, and in some cases thymus and adrenal cortex. Pregnancy urine gonadotropin treatment should be started between the ages of nine and twelve, not before but nearer to the ninth than the twelfth year, as the testis can be damaged if it remains in the scrotum after the ninth year. Intensive treatment for a short period is the best procedure, intensity depending on individual reactions. In some cases 3,000 to 4,000 rat units of pregnancy urine gonadotropic factor are sufficient, but in others as much as 18,500 rat units have been necessary. Many of the recorded failures are due to too low a dosage. The patient should be watched closely for symptoms of precocious puberty. The combination of pregnancy urine gonadotropin with other endocrine preparations and general constitutional methods is the essential treatment, which thus goes far beyond A. P. L. injections.

Failure of this treatment indicates an inflammation or a deep constitutional element. Recourse to surgery is then necessary, but attempt at surgical treatment of undescended testicle before a course of endocrinotherapy should be regarded as a serious error. Endocrinotherapy prepares the patient for surgery, and is necessary after operation also for correction of the hypogonadal and other coincidental disturbances of cerebro-pituitary infantilism.

Differential Nosography.

Thyroid and Pancreatic Infantilisms. In thyroid infantilism the characteristic triad microsomia, hyposexuality and mental retardation are determined predominantly by a hyposthenic reaction of the thyroid system. This system itself contributes to the development of stature, sexuality and mentality, and thus its deficiency may depress development of these functions even though the pyone and gonadal systems may not be involved to any important extent. There is always secondary inhibition of the phyone and gonadal systems, however, and thus physiopathologically and clinically this form can be isolated only on the question of predominance. The physiopathology explains the existence of so many intermediates between cerebro-pituitary infantilism, *i.e.*, combined hypophyonism, hypogonadism and hypothyroidism with a strong thyroid component, and thyroid infantilism, *i.e.*, a hypothyroidism with secondary involvement of the phyone and gonadal sys-

tems. Clinically and therapeutically thyroid infantilism is dominated by the syndrome of thyroid deficiency.

In pancreatic infantilism, so frequent in pre-insulin days, the hyposomia, hyposexuality and mental retardation constituting this disease are determined by hypo-insulinism, which through the cellular metabolic disturbances it causes retards growth, sexual and mental development. In this form also the phyone, thyroxin and gonadal systems play only a secondary role.

Malnutrition Infantilisms. This is an infantilism determined by a disturbance of the nutritional regulators of constitution. Retardation in growth, sexual and mental development is caused by the direct action of malnutrition on the metabolism of the various body cells and not by any action of these factors on the phyone, gonadal and thyroxin systems. Here again it is a question of predominance, and there are many forms intermediate between purely nutritional infantilism, which is a direct cellular infantilism, and cerebro-pituitary infantilism, in which malnutrition has upset the phyone, gonadal and thyroxin systems. Both mechanisms may coincide.

The general picture is that of cerebro-pituitary infantilism with certain special clinical shades.

General malnutrition and digestive disturbances dominate the etiology. Microsomia is constant but not very marked. Thinness reaching cachexia is an essential characteristic. Mental retardation is not severe, and usually only a low degree of intellectual obnubilation is observed. Infantile mannerisms are not usually apparent. Hyposexuality also is constant.

Malnutrition infantilisms include those determined by digestive disturbances, such as intestinal infantilism.

Treatment is essentially dietetic and hygienic. Endocrinotherapy is indicated for its metabolic effects. Growth hormone, testosterone, and to a slight extent chorionic gonadotropins are somatotropic, anabolic in particular for protein, and thus give great help in this condition. Thyroid and cortin should be avoided. The latter hormone has been used for many cachexias but is in fact indicated only in those with a hypo-adrenal element. Intensive vitamin therapy is a basic procedure. The best results are obtained from parenteral *B*-complex administration, but other vitamins must also be used according to the individual indications.

Deep Constitutional Microsomia. This is a biotype, or in accentuated cases a disease, determined by disturbance of the genetic regulators of growth. The defective gene acts on all cells of the body and slows their growth metabolism or sets up defective organisers for growth of the various segments. These individuals have a gene for microsomia as others have, for example, a gene for blue eyes. The microsomic gene may be transmitted hereditarily as a dominant, more rarely as a recessive, factor. In other cases there is a gene mutation, which explains sporadic deep constitutional microsomia.

Essential deep microsomia is sporadic, familial or racial. Racial microsomia is interesting from the anthropological point of view. The Akkas of the sources of the Nile, identical with the pygmies of Herodotus and Aristotle,

reach a height of 4 feet 7 inches. The average stature of the Bushmen is 4 feet 6 inches. In certain Pacific islands Max Berliner found races whose height varies between 3 feet $11\frac{1}{2}$ inches and 4 feet 1 inch. It is possible, however, as Sir Arthur Keith holds in the case of the Japanese, that some of these racial microsomias may be endocrine, *i.e.*, pituitary. Here statural diminution is caused by a disturbance occurring at the endocrine stage of human development, not at the genetic phase, and is due not to a primary disturbance of a general genic function but to a defective gene for the phyone system.

Clinically, diminution in stature with normal body proportions is the presenting symptom. In some cases the height shows merely slight deviations from the normal, as in certain racial and familial microsomias. In other cases the microsomia is much more marked than in all other forms of microsomia, including pituitary cases, and reaches the proportions of dwarfism. It is probable that Lilliputian dwarfs are sporadic deep constitutional or genetic dwarfs. Many such dwarfs are extraordinarily small. The earliest authentic English dwarf was John Jarvis, page to Queen Mary, whose height was 2 feet. Jeffrey Hudson (1619-1682), in the service of the Duke of Buckingham, is probably the smallest man in history. His height was 1 foot 6 inches, but at the age of thirty, following hardships due to his capture by pirates, he is said to have increased suddenly to 3 feet 9 inches. "General" Tom Thumb (Charles Stratton), shown in exhibitions in England in 1844, was 2 feet 7 inches.

Proportions are normal. These dwarfs and microsomics are eurythmic, thus differing from hypophyonic and other microsomes. They are men or women in miniature, men or women seen through the wrong end of the opera glass. Eurythmic microsomia is often called the "Lorain type," but the term has caused great confusion.

Therapeutically, within the frame of general constitutional measures, growth hormone injections give good results. Experimentally growth has been obtained in some racial dwarf mice, and clinically some good (but not excellent) results can be achieved by this method. I have seen it increase the growth of a Welsh girl of distinct familial (and racial) microsomia, but of course successes are much rarer than failures, probably for lack of adequate preparations.

Osteogenic Microsomia. This results from metabolic disturbances of the bones inhibiting the development of the bones of the limbs. These disturbances may be genetic as in achondroplasia and osteogenesis imperfecta, or acquired by means of various factors as in rickets, dwarfism and renal dwarfism. This group is therefore far from homogeneous.

Achondroplasia is probably the most interesting variety. Here the gene or gene complex regulating the endochondral ossification of the long bones, and thus growth in length, is pathologically modified, and the diaphyso-epiphyseal cartilages therefore develop irregularly with resultant defective development of bones.

The morphology is characteristic. The diminution of stature bears princi-

pally on the limbs, which have thick bones. In early life, radiological examination shows the line of the diaphyso-epiphyseal cartilages to be long and narrow. The cartilage cells are irregularly arranged and few. Hands and feet are short and thick. The hand is of trident shape with fingers of equal length but diverging. The head is very large with prominent forehead. The bridge of the nose is depressed from premature tribasilar synostosis. The vertebræ are flattened. Lordosis and abdominal protrusion are striking. In young subjects saddleback due to prominence of the buttocks is noted.

Psychological features also are interesting. Achondroplastics are usually clever and quick. Conscious of their deformity, they try to compensate by various " limelight features." Many court jesters of olden days were achondroplastic dwarfs, and many contemporary clowns belong to this constitutional biotype.

Renal dwarfism is another variety of osteogenic dwarfism. Here also the bone lesions, remotely resembling those of rickets (hence the term renal rickets) are responsible for the diminution in stature. Renal lesions dominate the clinical picture. The physiopathology of this condition is much discussed. Many authors regard the bone lesions as secondary to the renal disturbance, but others believe that both the osteopathy and nephropathy depend on a diencephalo-pituitary disturbance (Chown and Lee).

Fragilitas ossium shows a special clinical picture of multiple and easy fractures, and is associated with blue sclerotics. In rickets, dwarfism is due to vitamin D deficiency; other features of rickets coincide.

Treatment depends on the particular form. Achondroplasia enters more into the practice of the endocrinologist, and in its early stages can be treated with growth hormone, which permits a slight increase in height. Orthopædic treatment is important in these early cases. For adult achondroplastics nothing can be done.

CHAPTER XLIII

PITUITARY CACHEXIA

(SIMMONDS' DISEASE)

Physiopathology and Etiology.

This is a cachexia determined by the deficiency of various neuro-hormonal systems centred in the antepituitary. It is a combination of hypophyonism, hypothyroxinism, hypogonadism, hypocortinism, and hypodiabetogeninism. The first description was given by Morris Simmonds, of Hamburg, in 1914, who connected such cachexias with the pituitary. Urecchia and Elekes substituted a hypothalamic origin, and recent work shows that the polyhormonal deficiencies occur either through factors acting on the pituitary centres of these hormonal systems (primary pituitary cachexia) or in the hypothalamic centres of the same systems (cerebro-pituitary cachexia).

The complete breakdown of these important regulators of constitution and metabolism causes profound disturbances in all metabolisms. Basal metabolism is lowered by the hypothyroidean element. The specific action of proteins also is diminished, probably through failure of a special antepituitary metabolic hormone. The uric acid in the blood is increased, for reasons not yet clear. Nitrogen balance is distinctly negative. Carbohydrate metabolism is deranged through diabetogenin deficiency; hypoglycæmia, increased carbohydrate tolerance and sensitivity to insulin are noted. The fat depots lose their fat. Salt and water catabolism and thus loss are accentuated as a result of the adrenocortical element.

In its complete form pituitary cachexia is a rare disease, although more often seen than is apparent from the publications. Many cases are not published, and an even greater number not diagnosed. In its incomplete and mild forms it is a frequent disease, as can be gathered from physicians who examine their patients in an endocrinological spirit.

Primary pituitary cachexia is caused mainly by infections acting primarily on a more or less predisposed antepituitary. Puerperal infections are most frequently incriminated. Pregnancy, even without infections, may cause this disease by an obscure mechanism. Sinus infections can spread to the anterior pituitary and should not be omitted from consideration. Tumours localised on the pituitary and destroying the gland have also been described as factors of primary pituitary cachexia. In the case of Riecker and Curtis a malignant adenoma of the pars intermedia was pressing on the anterior lobe. In the case of Aitken and Russell, pituitary cachexia resulted from a hæmorrhage into a pituitary containing a chromophobe adenoma. Trauma involving the pituitary has been described in some cases (Lisser and Curtis).

Cerebro-pituitary cachexia is determined by the usual interplay of diathetic and environmental factors. The diathesis is formed of general neuro-endocrine imbalance. The environmental factors which affect the diencephalon and disturb the hypothalamic foundations of the antepituitary system are (*a*) tumours pressing on the diencephalon; (*b*) infections localising on the hypothalamus and the meninges of the base of the cerebrum, such as encephalitis and basilar meningitis due to syphilis, tuberculosis or spread of a sinus infection; (*c*) mental factors, important in both severe and mild forms; general emotional strain can affect the diencephalon via the corticodiencephalic connections and determine a cerebro-pituitary cachexia; (*d*) dietetic factors such as deficiency of vitamin E, which is necessary for normal function of the β-gonadotropin and the pituitary thyrotropic systems.

In these cerebro-pituitary cases a more or less accentuated atrophy of the antepituitary is found, but often no lesion at all. The antepituitary secreting cells may be inhibited without giving rise to any morphological manifestations.

Symptomatology.

The Complete Form. After an acute infection post-partum, or even without apparent cause, the patient begins to lose weight, and in women menstruation stops. The weight drops heavily and intractably until extreme

cachexia is reached. The patient ages in appearance, the skin becomes bluish-grey and other symptoms soon appear.

When the disease is completely constituted a rich symptomatology involves the morphological aspect and all functions of the organism.

The morphological features are the most striking. They consist in cachexia and senile aspect.

Cachexia in distinct cases is often extreme, a weight of four stone having been reported in adults. The patient seems made entirely of skin and bones, and the abdomen gives the impression of parchment stretched tightly over bones. Fat seems totally absent and the muscles are intensely atrophic. The senile aspect is distinct and in sharp contrast with earlier photographs of the patient. It is due largely to the skin, which lacks elasticity, shows deep wrinkles from the hypothyroxinic element of the disease and is of blue-grey melanotic pigmentation, probably because of the hypo-adrenal element. The scalp hair falls, and in some cases pubic and axillary hair also. Some of these patients have a hairy wool-like covering over the whole body. This, once considered as happening only in anorexia nervosa, has been demonstrated lately for all cases of Simmonds' disease. According to Sheldon, it is due to a reaction of the organism via the adrenocortical system, with the obvious teleological significance of assisting body heat. It has been encountered as a reaction to the consequences of starvation and described in the Irish Potato Famine of 1845. Teeth also fall—one of the most constant features. In cases where the disease started before the end of the period of growth and is of long duration, the stature is diminished.

The sexual system is deeply disturbed. In women amenorrhœa is a presenting symptom. It appears early, often before distinct cachexia, and is intractable. The external genitals atrophy, and even the uterus shrinks. Men show early impotence, lack of libido, and shrinking of the external genitals.

Reactivity manifestations are important. Asthenia dominates. It is intense and disproportionate to the decrease of muscular mass and even to the cachexia, and is due to the hypocortinic element of the disease. Often these patients cannot leave their bed. Anorexia is fairly frequent and reaches high proportions. It appears often at onset but not as in anorexia nervosa before the morphological, sexual and other organic disturbances, although it may be manifest when these disturbances are not sufficiently advanced to be very apparent. Patients are chilly and often hypothermic, and perspiration is absent, these symptoms indicating the hypothyroxinic element of the disease. There is feeble resistance to infection through the breakdown of the most important metabolic functions.

Sensitivity to insulin is an important reactivity manifestation of the disease, and is due to the hypodiabetogeninic, thus hypoglycæmic, component. Its occurrence is a warning to the unwary who treat all cachexias with insulin.

Depression is the keynote of the psychology of these patients. It bears on the cerebral faculties, and amnesia is a characteristic and often initial symptom. It affects their attitude to life. They become lethargic, apathetic and un-

interested in their surroundings. They are drowsy during the day and often sleepless at night. Some cases show severe psychopathic phenomena of confusion or disorientation. These features are in contrast to the obstinacy and morbid energy encountered in anorexia nervosa.

Nervous and circulatory manifestations are the most characteristic organic repercussions. Attacks of convulsions or loss of consciousness due to the hypoglycæmic (hypodiabetogeninic) element are noted. Tetanic attacks occur as a manifestation of the hypoparathormonal component. Hypotension is constant and determined by the hypocortinic element. It is an Addisonian hypotension and is accompanied by other symptoms of cardiocirculatory hypofunction. Hypochromic anæmia is usual and is probably due to failure of the hæmopoietic hormone of the anterior pituitary, but is also the result of the general metabolic upset. An intractable constipation depending on the hypothyroxinic element completes the clinical picture.

Laboratory investigation shows diminution of basal metabolism, hypoglycæmia and inability of the body to retain salt and water. The diminution of the basal metabolism is a result of the hypothyroxinic element. Hypoglycæmia is due to the hypodiabetogeninism. Inability to retain salt and water, in opposition to the finding in pituitary obesity, is evidenced by Volhard's test. Hormone studies have not yielded any distinct facts.

The disease progresses slowly for years. Death occurs from coma. Reicher reported an exceptional untreated case lasting for 40 years. Modern methods of treatment have prolonged life and even cured the condition.

The Anorexia Nervosa Form. This was first described by Morton in 1694, then by Naudeau in 1789, but principally by William Gull, who in 1868 defined it as a disease arising from a morbid mental state which manifests itself as a revulsion from food. According to recent work this leads, as Sheldon puts it, to a brake on antepituitary function and thus to a cachexia of pituitary origin. The physiopathology of anorexia and Simmonds' disease thus possesses a common ground, but the special psychogenic disturbance at origin and the special psychological personality of the patient make for distinct differences in the clinical picture and the therapeutic handling, and thus for its differentiation from the common form of Simmonds' disease.

Anorexia marks the onset of the disease. Careful examination shows also that the anorexia has started in the course of a mental conflict, a parental tussle or a disappointment in love. In some cases the patient begins to diminish her food intake so as to reduce her weight, and continues the procedure. For a certain time the special morbid anorexia constitutes the whole symptomatology. The patient exhibits remarkable wilfulness and energy which Gull emphasised in his first description, a definite insistence on shunning food.

Progressively there appear symptoms resembling those of pituitary cachexia, and they are in fact symptoms of that disease inasmuch as they are determined by a secondary hypofunction, a " brake " involving the neuro-hormonal systems centred on or linked with the antepituitary. Cachexia with senile appearance, falling of hair or hypertrichosis, amenorrhœa, constipation, bradycardia. These

cases are distinguished from those of Simmonds' disease by the wilfulness and drive of the patient, contrasting with cachectic and prematurely senile appearance. According to some authors the axillary and pubic hair are well preserved, may become sparse but never disappear.

The Pituitary Leanness Form. Pituitary leanness, described by von Bergmann, is a mild form of pituitary cachexia, usually cerebro-pituitary. It is very frequent. The clinical picture includes leanness, often accentuated, asthenia, loss of appetite, frilosity, lack of perspiration (manifestations chiefly of deficient thyrotropic secretion), hypomenorrhœic manifestations amounting to amenorrhœa, insufficient libido and potency in men (manifestations of gonadotropic hyposecretion), and lowered basal metabolism.

Therapeutics.

Regulation of appetite and of nutrition in general is first of all indicated. The digestive functions must be helped, and gastric dyspepsia and constipation must be treated on gastroenterological lines. The role of psychotherapy is obvious, its object being to encourage the patient and achieve his nutritional re-education.

Endocrinotherapy is the basic method. Chorionic gonadotropin (Pregnyl, Gonan, etc.) gives excellent results in both men and women. Later growth hormone, which has important protein anabolic effects, must be used. Serum gonadotropin is particularly effective in women and regulates menstruation better than chorionic gonadotropin. Liver is a good adjuvant. Cortin is less indicated and should be used with care. The same applies to gonadal hormones, both œstrin and testosterone, because of their antepituitary depressant action. Glucose insulin is contraindicated.

Physical methods form the third group of therapeutic agents to be used. Ultra-violet irradiation with the carbon arc lamp and short-wave diathermy of the abdomen have given me the best results in the formes frustes of this condition.

Deep psychotherapy must be applied in anorexia nervosa, without, howver, neglecting endocrinotherapy.

Differential Nosography.

Thyroid, Gonadal and Pancreatic Cachexias. These are important endocrine cachexias. Hyperthyroidean cachexia, *i.e.,* cachexia in Graves' disease, is seen but never so pronounced as in pituitary cachexia. It may occur very early, often as the first manifestation of hyperthyroidism, or later when the full disease is established. It may occur also in the form of paroxysms of leanness developing in the course of a more or less distinct Graves' disease suddenly and rapidly with or without concomitant diarrhœa. Basal metabolism is high, and other symptoms of hyperthyroidism coincide. Its treatment is that of the basic hyperthyroidism.

Hypothyroidean cachexia, more a simple leanness than a true cachexia, may occur in young subjects. It is a special form of hypothyroidism. It is never very accentuated and is accompanied by symptoms ot nervosity. Basal

metabolism is low. It is treated with small doses of thyroid. Large doses are not tolerated.

Gonadal cachexia is encountered in certain cases of hypogonadism. It has been described in this work in connection with the " old eunuchoid," and is more frequent in the female.

Pancreatic cachexia is symptomatic of pancreatic diabetes and is due to the general metabolic upset caused by hypo-insulinism. It represents the old " diabète avec dénutrition " of French clinicians and is seen only exceptionally in the insulin era.

Lipodystrophia. Lipodystrophia is a disease of the nervous vegetative system resulting probably from a hypothalamic disturbance. Fat disappears from the upper part of the body, the infra-umbilical portion retaining its normal adipose tissue. The nervous vegetative disturbance affects the local lipophilia of the tissues.

Deep Constitutional Cachexia (Progeria). The clinical picture of pituitary cachexia is reproduced in a sort of caricatural exaggeration in a rare disease called progeria, which is determined not by a pituitary polyhormonal deficiency but by deficiency of the genes and organisers during development. Progeria stands in the same relation to pituitary cachexia as cretinism to myxœdema and the Laurence-Moon-Bardet disease to Fröhlich's disease.

Progeria, described by Hastings Gilford in 1904, is characterised by an impressive degree of the cachexia, dwarfism and senile appearance. A peculiar feature of hair and skin—lack of hair and a wrinkled, brownish and senile skin —is characteristic. This is probably due to a genetic disturbance of skin development and gives the characteristic senile aspect, mainly of the face, crystallised in the term by which this rare disease is known. Another characteristic feature is delay in ossification. Even the membranous bones of the skull fail to ossify normally, and for a long time the structure resembles the fœtal skull. Dentition, walking and talking occur late.

CHAPTER XLIV

PITUITARY ADIPOSOGENITAL DYSTROPHY

(BABINSKI-FRÖHLICH DISEASE)

Physiopathology and Etiology. This is known as Fröhlich's disease although the term Babinski-Fröhlich disease is more accurate. In 1900, Josef Babinski described a case of obesity with genital hypoplasia (*i.e.*, adiposogenital dystrophy) connected with a pituitary tumour, and pointed out a physiopathological relation between the pituitary disturbance and the disease. One year later, Alfred Fröhlich recorded a similar case in Frankl-Hochwart's clinic in Vienna. Several more cases were subsequently collected, and in 1908, Bartels designated the whole group as adiposo-genital dystrophy.

The primary physiopathological basis accepted first by Babinski and later by Fröhlich gave way to a cerebro-pituitary conception following the work of Roussy and of his collaborators, Camus and Mossinger.

It is accepted to-day that the physiopathological basis of Babinski-Fröhlich disease or adiposogenital dystrophy is involvement of two neuro-hormonal systems, the gonadal (male testosterone or female œstrin) system and the pituitary fat-metabolic system. This involvement originates in the hypothalamic centres of these systems. The gonadal hormonal disturbance is clearly demonstrated, and consists in hypofunction. The pituitary fat-metabolic disturbance is less distinct because so little is known about pituitary lipometabolins. There may be antepituitary lipoanabolin hyperfunction or postpituitary lipocatabolin hypofunction, both originating in the hypothalamic centres of these systems. It is possible also that the lipodystrophic element of the disease is determined by a purely cerebro-neuro-vegetative disturbance acting on adipose tissue lipophilia without any pituitary intervention.

Other neuro-hormonal systems can be involved through extension of the hypothalamic disturbance. Insufficiency of the thyroid, diabetogenin and antidiuretin systems is often noted. The phyone system may be normal or in hypo- or hyperfunction.

The principal metabolic disturbances determined by the dysfunction of all these endocrine regulators in Babinski-Fröhlich disease are defects in the biochemical processes of the cells constituting the genital system, and increase of fat formation in the depots. There are extensive changes, however, in the general chemistry of the body. Energy metabolism is diminished by a coincident hypothyroidism, often the sole manifestation of hypothyroidism. Hypoglycæmia occurs through an involvement of the diabetogenin system which allows the insulin system to act unchecked. Water catabolism is excessive when postpituitary antidiuretin is involved.

Cerebro-pituitary adiposogenitalism is a disease of childhood and early adolescence, although it may be projected into later stages of life. The term adiposogenital dystrophy indicates that the disease sets in before puberty. Hypoplasia of the genital organs associated with obesity occurring after sexual maturity has been attained should not be classified as adiposo-genital dystrophy.

One class of cerebro-pituitary adiposogenital dystrophies is due to tumours pressing on the hypothalamus, usually a chromophobe adenoma or a craniopharyngioma. Such were the first cases described by Babinski and by Fröhlich, but they are not regarded nowadays as very frequent. Another group of adiposogenital dystrophy is determined by infections acting either on the diencephalon (encephalitis) or on the meninges of the base of the brain (basilar meningitis). Syphilis and tuberculosis are the most important of these infections. In a case of Hval adiposogenitalism was caused by a combination of chronic peripituitary meningitis involving principally the postpituitary, and a gumma of the anterior lobe. Most frequently, however, the basic factor in the disease is a genogenic inferiority of the gonadal and fat-metabolic neurohormonal systems, which are thus easily upset by the endocrine storms of

puberty and by psychogenic and nutritive factors (particularly over-nutrition, especially of sweets). This genogenic inferiority explains the familial and hereditary incidence of Babinski-Fröhlich disease. Some exceptional cases of the disease following trauma have been described, such as that of Frank in which a bullet reached the sella turcica, and that of Cushing whose patient had sustained severe cranial injury.

Clinical history. Occasionally the disease is ushered in by tumoral symptoms, headache and visual disturbances. Obesity usually signals the start of the disease, however, and as the young are afflicted this symptom is more striking than genital disturbances. Developmental disturbances bearing on walking, ossification, dentition and intellectual progress occur when thyrotropic secretion is impaired.

Obesity and other morphological features. The girdle obesity, the most characteristic feature, is similar to that described in pituitary obesity. Fat accumulates on hips, abdomen and breasts (often in boys as well as girls). The extremities remain thin.

Stature varies, being above normal, normal or sub-normal, according to the involvement of the growth hormone system. Eunuchoid proportions, *i.e.*, macroskelia, are usual but not constant.

The general appearance is infantile, and in boys feminine. The face is small with delicate features which appear alert and cherubic The delicate skin, atrophic when the growth hormone is involved, is a " peaches and cream " complexion on account of its vascularity. The bridge of the nose is straight. The teeth show gaps and are often of miniature size. Radiological exploration shows rudimentary sinuses and scanty diplœ. This facies contrasts sharply with the coarse homely features and deeply saddled nose of the myxœdematous and the strong features of the hyperpituitarian.

The hands and feet are small, a remarkable feature in persons of otherwise generous proportions. The fingers are tapering and show hooking on radiological examination. The nails are small and delicate with very small lunulæ. Genu valgum is frequent.

The skin is very delicate and thus liable to infections and very susceptible to external influences such as heat, sunlight, wind and dust. It is sometimes pigmented, chloasma occurring as a result of disturbance of the intermediate lobe of the pituitary. The most notable characteristics, however, are striæ and dimples, distinct pituitary manifestations. The striæ are red or white and comparable to those seen in pregnancy. The dimples are irregular and shallow. Both striæ and dimples are very marked and mar the æsthetic appearance, particularly in girls.

Hair is generally undeveloped except on the head. Pubic and axillary hair appear late, and in both boys and girls the pubescence ends in a transverse line. Boys do not develop hair on the face. In rare cases, however, hypertrichosis has been described even in females.

Sexual hypoplasia and hypofunction. Hypogenitalism dominates. In males the external genitals are hypoplastic and ectopic testicle is noted in some

cases. Puberty does not occur normally, but is retarded and incomplete. Lack of potency, libido and fertility are noted later. In females the genital hypoplasia is difficult to assess but functional disturbances are more distinct as they centre on menstruation. Menses occur very late, are scanty and occasional, although menorrhagia from luteostimulin insufficiency may be met. Dysmenorrhœa is very common, and is probably another result of luteostimulin insufficiency. It occurs sometimes in the form of pain in the lower right quadrant and has been mistaken for appendicitis. Later, lack of libido, diminished fertility and abortive pregnancies are noted.

The mental syndrome. This looms large in the symptomatology of Babinski-Fröhlich disease. It is due in part to environmental factors of parental pampering, in part to the hormonal deficiencies which react on the metabolism of the cerebral cortex, and in great part to an abnormal psychological defence reaction to the disease.

Sluggishness, languor, apathy and some degree of mental retardation are leading features in one group of cases, and are due mainly to the hormonal deficiency. The sluggishness may amount to simili-hibernation. The mental retardation, when hypothyroidism does not complicate the picture, is not very marked. It is a product of the sluggishness and laziness, and the essential manifestation is inability to concentrate, not absence of intellectual power.

Submissiveness, introversion and emotionality is another group of mental features, often coinciding with the preceding features or dominating the clinical picture. Submissiveness is a hypogonadal manifestation. Such children are shy, clinging, easy-going, and their attitude to life is one of compliance. They are nice sweet children who avoid all competitive work. Introversion also is due to the hypogonadism but a psychogenic factor of a feeling of inferiority intervenes. These children avoid playmates, who jeer at them, and find refuge in a life of fantasy and day-dreaming. They become self-conscious and are unwilling to associate with their companions in sports, especially in those, like swimming, which entail exhibition in the nude. Emotionality is a feature of both hypogonadism and hypothalamic disturbance. These children are often extraordinarily sensitive and for the slightest reason believe that their parents do not love them. Boys cling to their mother in a sort of hormonal Œdipus complex. Girls cry easily when hurt mentally or physically. Emotionality quickly merges into the irritability often manifested by nail-biting or gnawing inanimate objects and violent fits of temper on the smallest provocation.

Craving for the limelight develops as an anti-social reaction to the sense of inferiority. Such children do foolish things so as to attract attention. They steal, they lie, they develop feelings of hostility against the society that has caused them suffering. They replace the submissive feminine attitude which results directly from their hypogonadal disturbance by an aggressive, often sadistic, attitude of purely psychological origin.

Background symptoms. As in all endocrine diseases, symptoms are spread over all functions and organs of the body. The reactivity of these patients

is ruled by asthenia, or rather a laziness, often linked with their easy-going temperament. Ravenous appetite and a particular desire for sweets is another striking reactivity feature due probably to hypoglycæmia. I have seen big boys cry when telling of their craving, which their parents do not allow them to satisfy. Lurie tells of a boy who took to stealing in order to satisfy his longing and was referred for medical examination by the juvenile court.

Nervous symptoms, particularly headache but also giddiness, somnolence and epileptic attacks are noted. They may be due to pressure of a causal tumour on the hypothalamus but are usually of hormonal origin. Digestive symptoms also are frequent because both lobes of the pituitary regulate digestive functions. Atonic dyspepsia and constipation with tympany are often noted, as well as chronic intractable abdominal pain simulating cholecystitis and chronic appendicitis which has led to many unnecessary operations. Acute abdominal attacks occur here as in thyroid and diabetic-acidotic states, and are another source of needless operation. The endocrine abdomen should enter into differential diagnosis. Circulatory disturbances are comparatively unimportant in these young subjects, but marked in older persons with pituitary obesity. However, tachycardia and hypotension often exist, and are related to the disturbance of the cerebro-pituitary regulation of the circulation.

Tumoral symptoms appear in neoplastic cases. From this point of view ophthalmological and radiological investigation is necessary in adiposogenital dystrophy.

Laboratory exploration shows the metabolic disturbances delineated in the physiopathology but nothing absolutely characteristic. A low basal metabolism indicates a hypothyroidean element. The specific dynamic action of proteins is diminished, a distinct antepituitary manifestation. Hypoglycæmia and increased carbohydrate tolerance, investigated by alimentary glycosuria and indicating diabetogenin deficiency, are frequent. Retention of salt and water occur as manifestations of posterior pituitary hypofunction. Hormonal studies have yielded no definite data.

Course and termination. Neoplastic pituitary adiposogenitalisms depend as to course and termination on the development of the tumour. Of non-neoplastic conditions pre-adolescents are curable to an extent depending on the severity and duration of the endocrinopathy and the adequacy of treatment. As in all endocrine states, failure to correct the defect in time leads to ill-health and a premature old age. Over-treatment, however, must be avoided, particularly in cases occurring towards puberty, which are caused by the endocrine storm of puberty and retrocede, often spontaneously, or at all events with simple constitutional measures.

Therapeutics. Dietotherapy is important, and a dietary on the linesdescribed for cerebropituitary obesity is necessary. There must be no exaggeration, however, for the obesity of Babinski-Fröhlich disease, cerebro-pituitary obesity and most obesities are not solely problems of caloric intake and spending.

Kinesitherapy, crenotherapy and other physical methods are used as in cerebro-pituitary obesity.

Endocrinotherapy is a delicate method in this condition. The hormones in use are pituitary gonadotropic, pituitary whole gland, thyroid and pituitrin. Thyroid is always useful not only because of the coincidence of hypothyroidism but for its general metabolic effects. Pituitary gonadotropin or similar preparations (pregnancy urine gonadotropin and pregnancy gonadotropin serum) are useful for the gonadal hypoplasia but have no definite effect on the obesity. Pituitary whole gland in strong doses (2·0–3·0 per diem) has given me good results but unfortunately remains very expensive. It is safer to test the sensitivity of the patient, beginning with small doses of, say, 0·05 per diem, for in some cases this medication causes headache—despite the contention of some laboratory workers that pituitary is not absorbed by the digestive tract. Pituitrin skilfully used gives good results. From the clinical point of view the dosage can be graded into three: (*a*) the degree that produces only vascular reaction with pallor and greenish discolouration of the skin, under half a cubic centimetre for the adult; (*b*) the degree producing intestinal reactions in the form of cramps, colic and defæcation, one-half to one cubic centimetre for the adult; (*c*) the degree producing a general reaction with tachycardia, palpitations, syncope with marked emotional and psychical symptoms, over one cubic centimetre. The figures given are only approximate, for there are many special idiosyncrasies to pituitrin. In the Babinski disease a dosage which falls short of producing intestinal reactions should be given.

Cortin is employed by some authors for its masculinising properties (feminism existing in this disease) but I have never obtained any good results, although I use adrenal cortex in combination with pituitary whole gland and thyroid for oral treatment. Laxatives are important, but in my opinon diuretics are better avoided.

Differential Nosography

Laurence-Moon-Bardet Disease. This familial and congenital disease was first described by John Zachariah Laurence and R. C. Moon in 1866, but the condition attracted no attention until in 1920 it was re-described by Bardet in his Paris thesis "On a syndrome of congenital obesity with polydactyly and retinitis pigmentosa." Biedl reported two cases in 1922, and in 1928 Boenheim added nerve deafness and cutaneous pigmentation to the clinical picture. The earlier authors attributed the condition to a pituitary disturbance, but recent work, particularly the memoir of Cockayne, Krestin and Sorsby in 1935, demonstrates its genetic physiopathology.

It is not known whether one abnormal gene is sufficient to produce the whole condition or whether the disease is the result of multiple gene anomalies. The one-gene conception seems the most feasible according to the modern principles of genetics. From the heredity point of view this gene is autosomal recessive.

This pleiomorphic gene (or gene complex) disturbs metabolism during development in such a manner as to determine the whole symptom complex. It is interesting to note that besides subcutaneous tissue lipophilia the causal gene determines lipoid histocytosis, a factor in macular degeneration, found also in the cerebrum in amaurotic iodiocy. This shows the connection between lipoid histocytosis and subcutaneous tissue lipophilia, which is in fact a lipoidosis. The pituitary does not seem involved. No necropsy has been made but most of the skiagrams have shown no change in the sella turcica.

The clinical features are the following: (*a*) Obesity, generalised rather than of the girdle type; (*b*) genital hypoplasia; (*c*) mental deficiency, in 60 out of 72 cases according to Reilly and Lisser; (*d*) retinitis pigmentosa, more or less typical; (*e*) polydactylism.

Familial incidence is frequent but not constant. Reilly and Lisser find it in 25 out of their 77 cases. The disease is relatively rare. In 1935, 108 cases were collected by Cockayne, Krestin and Sorsby.

CHAPTER XLV

CUSHING'S DISEASE

Physiopathology and Etiology.

In 1932, Cushing described this particular disease, which he connected with a pituitary basophile adenoma or a pituitary basophilism. The clinical picture delineated by this master remains intact, but the physiopathology has given rise to many discussions. A safe working conception is that Cushing's disease is a hypersthenic reaction of the adrenocortin system involving many factors of this system, principally the sex masculinising factor (sex steroids) and the carbohydrate factor (the sugar steroids) combined with a special tissue reactivity.

This hypersthenic reaction may originate in the diencephalic centre of this system. Heinbecker has found in this disease changes in the hypothalamic nuclei, particularly the paraventricular nuclei. The hypothalamic disturbance affects the basophiles of the pituitary and causes hypersecretion of adrenocortin, and Heinbecker has found in his experimental work that following lesions of the hypothalamus there occurs the hyalinisation of the basophile cells (Crooke's lesion) characteristic of Cushing's disease. Following this excessive adrenotropin, hyperfunction with or without hyperplasia occurs in the adrenal cortex.

The hypersthenic reaction may originate in the pituitary centre of this system from a hypersecreting basophile adenoma. Here also hyaline degeneration of the basophiles is encountered, but in the cells outside the adenoma.

Here also hyperfunction with or without hyperplasia occurs secondarily in the adrenal cortex.

Finally, the hypersthenic reaction may originate in the adrenal centre of the system in a hypersecreting adrenocarcinoma.

Enlargement of the thymus and cancer of the thymus have been described in Cushing's disease, but in all cases hyperplasia of the adrenals coincided. As the pituitary possesses a thymotropic hormone, which may or may not be identical with growth hormone, there may be a coincident hypersecretion of this hormone of primary pituitary or cerebro-pituitary origin. Parathyroid hyperplasia also has been encountered (Kessell, Lawrence and Zimmerman), and this may be explained by a coincident hypersecretion of parathyrotropin.

Cerebro-pituitary Cushing's disease is essentially determined by a genogenic lability of the adrenocortin system, which thus enters into imbalance with the usual stress of life or following more distinct factors such as the metabolic changes caused by gonadal disturbances, mainly menopausis and pregnancy. In a case of V. Cohen Cushing's disease developed in the course of pregnancy with pernicious vomiting, progressed to an extreme degree and retrogressed after spontaneous abortion. The work of Selye on the adaptation syndrome gives the key to these cases. Adrenocortin hyperfunction occurs following various non-specific conditions of shock and stress and sometimes persists long after the initial stimulus has ceased to exist.

In primary pituitary Cushing's disease the polyhormonal hyper-secretion originates in a basophile adenoma of the antepituitary. Basophile adenomas are small tumours, measuring about 2 mm. in diameter, constituted of basophile cells. They rank next in frequency among pituitary tumours to chromophobe adenomas and therefore occur more often than eosinophile adenomas. Most basophile adenomas are silent clinically but a few give rise to Cushing's disease. Cushing's disease has also been observed with chromophobe and eosinophile adenomas of the antepituitary (Salus, Fuller, Russell). This physiopathological mechanism is obscure.

Primary adrenal Cushing's disease results from an adrenocortical carcinoma of obscure etiology which seems, however, to be connected with neurohormonal disturbances.

Hypersecretion of the carbohydrate factor of the adrenocortin system, probably coinciding with hypersecretion of the pituitary diabetogenin, causes intense gluconeogenesis and thus, besides hyperglycæmia and glycosuria, intense loss of protein, because protein is used for this sugar formation. The protein paucity explains the comprehensive tissue atrophy, the thinness of the skin, the tendency to bruise and the muscular weakness of these patients. It may explain also the osteoporosis, because in Cushing's disease, according to Albright, osteoporosis is due to lack of bone matrix and not to a disorder of calcium metabolism. Hypersecretion of the sexual factor of the adrenocortin

system determines the special masculinisation and probably the special obesity of male distribution.

Hypersecretion of the electrolyte factor (the salt steroids) also occurs. It explains the metabolic findings of McQuarrie and probably the hypertension.

Symptomatology.

Female Cushing's Disease. Whatever its etiology, the clinical picture of Cushing's disease is the same, differing only according to sex. Female Cushing's disease is more frequent than its male counterpart and more typical. Onset is marked by a change of appearance, a tendency to develop a moon-face (striking in women), an obesity developing rapidly, amenorrhœa, polyphagia, polydipsia.

Presenting symptoms. These are obesity with virile aspect, osteoporotic cyphosis and osteoporosis in general, thinness of skin with striæ distensæ, amenorrhœa, diabetes, hyperpiesia.

The obesity with virile aspect contrasts with the cachexia and senile appearance of Simmonds' disease. It is acquired rapidly and reaches fairly high proportions. It is often painful. It is marked on the face, to which it imparts the full-moon appearance more characteristic of Cushing's disease than of myxœdema, with which it has been erroneously linked. It is marked also on neck and trunk, and in general is an upper obesity, from umbilicus upwards, constituting an exaggeration of male fat distribution. It is a plethoric obesity, hard to the touch. In rarer cases a girdle obesity or " pituitary " type has been noted, and is usually not a real girdle obesity but only an extreme relaxation of the abdominal muscles giving the false impression of accumulation of fat in that region. The virile aspect is distinct in the facial expression and in the distribution of hair, which develops fully on body and face (femmes à barbe) but disappears to some extent from the scalp, causing real calvities in some cases. This obesity with virilism is determined by the hypercorticogenitalinic element of Cushing's disease.

Osteoporotic cyphosis and osteoporosis in general is determined by the hyperdiabetogeninic element of the disease, and does not call for postulation of hyperparathormonism. Cyphosis is a striking morphological feature. It is cervicodorsal and is caused by the crushing of the osteoporotic cervithoracic vertebræ. Osteoporosis is noted radiologically in other parts of the skeleton.

The thinness of the skin contrasts with the gerodermic aspect of Simmonds' disease. To this thinness is due the reddish hue of the skin, as the dilated cutaneous vessels are visible through the fine skin. The thinness also causes the striæ distensæ, which result from the cracking of the friable skin. Easy bruising is frequent, and results from the poor resistance of the thin skin and from the friability of the small vessels, which have lost their pituitary metabolic control. Acrocyanosis is often seen. The skin is frequently dry, shows acne, and is liable to infections.

Amenorrhœa dominates the clinical picture as in Simmonds' disease, but for different reasons. It does not arise from a primary disturbance of the gonadotropic centres of the hypothalamus or the antepituitary, but by inhibition of these centres through excess of the antagonistic cortigenitalin.

Diabetes and diabetoid contrast with the hypoglycæmia of Simmonds' disease. It is often accompanied by polyphagia and polydipsia and is due to the hyperdiabetogeninic element in Cushing's disease. It develops in waves, often retrocedes without treatment, and is in general of mild form and resistant to insulin.

Hyperpiesia due to the cortipressin (salt steroids) element completes and often dominates the picture.

Background symptoms. To these six important groups of symptoms are added others constituting a background to the clinical picture. Asthenia is constant, and such patients tire very easily. Their muscular power in particular diminishes, often to an intense degree, and the muscular mass itself seems to shrink, as evidenced by the low creatinine excretion. Mental depression is the rule, and is due to the psychological reactions of the individual to his deformity. Three suicides in 58 verified cases of Cushing's disease with pituitary adenoma have been reported by Eisenhardt and Thomson. Polyglobulia is noted in some cases. Laboratory investigation shows the metabolic disturbances described in the physiopathology, principally diabetes or diabetoid. Excess of adrenotropic hormone has been found in the blood and increase of 17– ketosteroids in the urine bearing chiefly on dehydro-iso-ketosterone, which appears to originate in the adrenal cortex in both men and women.

Tumoral symptoms do not exist in neoplastic cases, as the basophile adenomas are usually very small, but some cases show enlargement of the sella turcica.

Course and Treatment. Mild forms are essentially chronic but distinct forms are progressive and shorten the life of the patient. Death occurs from circulatory manifestations, cerebral thrombosis, diabetes or hypopituitarism succeeding the hypersthenic phase that characterises the disease.

Œstrogen administration in strong doses and pituitary radiotherapy are the best methods of treatment. Œstradiol preparations can be supplemented by the local application of œstradiol ointment for hypertrichosis and other skin manifestations. Pituitary radiotherapy also is effective. Diet is prescribed on the lines of the obesity diet but need not be very severe. Diabetes in Cushing's disease is treated more by diet than by insulin, and yields particularly to a low calory diet. Proteins should be given in adequate quantity. The nervous system needs especial consideration with suitable psychotherapy and sedatives according to indications. Strenuous exercises, to which such patients often resort in order to reduce their weight, are not only useless but often aggravate the condition, and in general relaxation and rest are more beneficial.

Male Cushing's Disease. Plethoric or buffalo obesity is the dominant feature. This develops quickly. Patients, particularly males, gain from 25–50 per cent. of their body weight in six months. Fat accumulates on the upper part of the body, on face, neck, shoulders, arms and upper abdomen. Legs, thighs and hips remain untouched. The face is rubicund with a tendency to congestive cyanosis, and the skin of the face looks as though it would burst.

Intense motor activity characterises the reactivity of these patients and contrasts with their obesity. Sufferers from this form of obesity walk miles every day in an unsuccessful attempt to reduce their weight. Their intense activity is in striking contrast with the flabbiness of sufferers from hypothalamo-pituitary obesity, and with the easy-going laziness of sufferers from nutritional obesity.

Hypersexuality, with increased potency and libido exists at onset but later sexual exhaustion sets in.

The leading mental features are extravert attitude and cyclothymic reactions. Such patients are typical extraverts. They are always on the go, show a mental activity as exaggerated as the physical, and like to be in contact with their fellow beings. In many cases phases of great mental activity and exaltation alternate with phases of depression. This constitutes the cycloid reaction type which Kretchmer has shown as occurring in persons of pyknic habitus, which is in fact the adrenocortical habitus. Such patients develop cyclothymic psychoses (manic depressive psychoses) when other factors intervene.

Blood pressure, both systolic and diastolic, is high. The combination of hyperpiesia and plethoric obesity constitutes the apoplectic habitus of physicians of bygone ages.

The disease is essentially chronic and intractable. Cerebral hæmorrhage may occur at a later stage.

Treatment follows the lines indicated for cerebro-pituitary obesity but with greater insistence on nervous sedatives. Radiotherapy can be considered.

Differential Diagnosis.

Adrenal Virilism. In adrenal virilism the hyperfunction of the adrenocortin system involves nearly exclusively the sex masculinising factor. This explains the predominance of the masculinising factor and the absence of obesity, of special striæ and of diabetes in adrenal virilism. This condition can be cerebro-pituitary or primary adrenal. A basophile adenoma does not give rise to this simple form. Although there are many intermediate cases, the clinic and physiopathology differentiate these two diseases.

Hyperostosis Frontalis Interna (Morgagni-Stewart-Morell syndrome). This is a disease, probably with an endocrine basis, characterised by obesity, virilism, hyperostosis of the internal table of the cranium and often by mental disturbances. The special cranial bone changes differentiate the condition from Cushing's disease.

CHAPTER XLVI

CEREBRO-PITUITARY OBESITY

HYPOTHALAMIC OBESITY

Obesity is an accentuated storage of neutral fat in the depots, in other words, a pronounced lipophilia of the adipose tissue cells. Recent work, brilliantly reviewed by Wells, has shown that the adipose cells are active and probably belong to the reticulo-endothelial system. Obesity is essentially a neutral lipophilia, a special neutral fat or triglyceride lipoidosis, in the same manner as Gaucher's disease is a kerasin lipoidosis, Nieman-Pick disease a lecithin lipoidosis and Hand-Christian disease a cholesterol ester lipoidosis.

The basic disturbance is thus a disturbance of the special enzyme of the adipose cell, the special lipase which normally is able to dissociate fat into fatty acid and glycerine and conversely to combine these elements into fat.

The capacity of this enzyme is regulated by its genetic constitution, but also by the neuro-vegetative system acting directly on the cells and by certain neuro-hormonal systems which stimulate or inhibit the transference of fat from the depots to the liver and its elaboration in the liver (pituitary fat-metabolic hormones, lipocaic, liver enzymes), and by those neuro-hormonal systems which stimulate or inhibit fat oxidation in the peripheral tissue. It is regulated also by external factors of nutrition and movement. Over-nutrition surcharges the depots. Sedentarity does not demand from the adipose cells the release of their fuel.

A genetic deficiency of the adipose cell lipase or a deficiency of any of the regulators enumerated above causes obesity.

Hypothalamic, hypothalamo-pituitary or cerebro-pituitary obesity is determined primarily by a disturbance in the fat-metabolic centre of the hypothalamus, acting either by increasing the lipophilia of the fat depots via the vegetative nerves going to these depots, or by influencing the secretion of pituitary fat metabolic hormones which regulate transport, hepatic elaboration and peripheral oxidation of fat.

Hypothalamic disturbances have been demonstrated to cause obesity by many experiments (Camus and Roussy, Ransom, Fischer and Ingram) and clinical observations (Eaves, Greene, Lhermitte and many others). Various experimental and clinical observations have shown that such disturbances can cause obesity by increasing tissue lipophilia through a purely nervous action. Thus, a local adiposis has been produced experimentally by injury to the sciatic nerve (Mansfeld and Muller). Lipomas have been reported after injury to the spinal cord (Buschke and Casper). Lipomas usually show a symmetrical disposition manifesting nervous localisation. Hemiatrophy of the face, which may be limited to atrophy of fat tissue (although in the majority of cases it involves skin and bones as well) coincides with clinical manifestations pointing

to a nervous lesion, and is in fact encountered in lesions of the cervical sympathetic, particularly of the superior cervical ganglion.

PITUITARY OBESITY

Hypothalamic disturbance can cause obesity by influencing the secretion of pituitary fat-metabolic hormones. This has been known ever since the clinical observation of obesity associated with pituitary lesions (principally since knowledge of the Babinski-Fröhlich disease) but the mechanism is as yet obscure. Hypophysectomy causes cachexia, not obesity, but it is possible that lesions more localised in the posterior pituitary determine obesity. Clinically, pituitrin injections have good therapeutic effects in certain obesities, and there is some experimental evidence of the existence of a postpituitary fat-metabolic hormone.

There is a third mechanism through which a hypothalamic disturbance can cause obesity, namely, increase of appetite after disturbance of the appetite centre of the hypothalamus. Hetherington and Ransom have noted a greater food intake in rats with hypothalamic lesions. This mechanism links this form of obesity with the nutritional obesities already described.

Hypothalamo-pituitary obesity results from encephalitic lesions and tumours pressing on the hypothalamus, and as a secondary reaction to hypogonadism. "Gonadal obesity" in fact represents a special reaction of the

pituitary fat-metabolic hormone system to hypogonadism. This last etiological form occurs after pregnancy, at the climacteric and in various states of hypogonadism. A genogenic inferiority of the hypothalamic fat-metabolic centres is an important factor.

The Common Form. Hypothalamic obesity is gradual at first and rapid thereafter. It reaches enormous proportions—in fact, all monstrous obesities are hypothalamo-pituitary. It may occur after infections, and is then determined by an encephalitic localisation, not by the over-nutrition of convalescence. It is seen after pregnancies and at the climacteric.

The distribution of fat is characteristic, and summarised in the term " girdle obesity." It affects abdomen, hips, thighs, mons veneris. Fatty masses over the trochanter are very marked, and in some cases adiposis is limited to that area (trochanteric obesity). Abdominal adiposis is very considerable and in severe cases the lower abdomen forms a large fatty fold which hangs down over the genitals like an apron.

Besides the girdle region other parts of the body may be invaded by adiposity. Mammary adiposis is frequent and pronounced in women as well as in men. The upper neck is involved and a double chin formed. Sometimes masses accumulate in the deltoid region. The face, however, is normal, and the extremities are free of adiposity, which cuffs off in the middle of thigh and arm. The hands show no dorsal padding, and no supraclavicular padding develops. On the whole, these patients resemble the favourite models of Rubens.

The adipose masses give the impression of flaccidity and coldness, differing in this respect from the fat of healthy subjects. In some cases they may be painful, constituting Dercum's syndrome. Dimples mottle the outer sides of the thighs and the gluteal region, and white or reddish striæ comparable to those appearing on the abdomen after childbirth and ascites are often seen. The striæ have a distinct pituitary stamp, and are not always due to loss of flesh but depend on a trophic disturbance under pituitary influence.

Such patients are characterised by many hypothalamic manifestations as well as by the form of the obesity. The chief of these manifestations is hyperemotionality, which contrasts with the phlegmatic or " bon vivant " stamp of nutritional obesity. The hyperemotionality is based on the important role of the diencephalon in the genesis of emotions, and possibly on the influence of the pituitary on bromine metabolism. These patients are highly strung and loquacious, take life too seriously, and vibrate intensely to all mental stimuli, especially those touching their person. They develop anxiety as a special exaggeration of their hyperemotionality, and centre it on their cure. For this reason they are difficult to treat regularly because their impatience impels them to rush from one treatment to another, change physicians and try any quack remedy of which they hear. All this aggravates their condition, which for cure needs mental rest and confidence. Irritability, sadness and depression also result from the hyperemotionality. Their irritability, however, gives rise

to fits of anger but not the apoplectic behaviour of adrenal obesity, and their sadness, although occurring in waves because of its neuro-hormonal character, does not assume the cyclothymic form which also characterises adrenal obesity.

Sleep disturbances, although rare, can add to the hypothalamo-pituitary stamp. In mild forms daytime drowsiness is combined with sleeplessness at night. In severe forms a real narcolepsy may be observed. These disturbances are connected with the role of the hypothalamo-pituitary system in sleep.

PITUITARY OBESITY

Next to hyperemotionality and dyssomnia asthenia indicates the hypothalamo-pituitary nature of this disease. This symptom, common to so many endocrinopathies, is here accentuated by the necessity of transporting a large body mass and by the circulatory disturbances frequent in such patients. It is not the easy fatigability or the paroxysmal weakness of Addisonians, but a continuous fatigue which prevents the patient from carrying on as efficiently as before his disease. The daily productivity decreases gradually. The slightest action demands great effort and in spite of that effort the result is meagre and deepens the discouragement felt by the patient.

The other general symptoms offer no peculiar features. Perspiration is free and often even abundant. It is due to the considerable exertion used in movement by bulky persons and to nervousness. There is a particular lack of

resistance to infections, principally to pneumonia. The sexual condition is low in forms secondary to hypogonadism, but varies in others.

The organic symptomatology is dominated by cardiocirculatory disturbances, which are a special feature of the cerebro-pituitary form of obesity. They are not due solely to fatty infiltration of the heart but mainly to lack of circulatory regulation by the posterior pituitary. Pressure is low, palpitations and effort dyspnœa are frequent, and various degrees of heart insufficiency occur. Sufferers from pituitary obesity die of heart conditions.

Nervous symptoms are very frequent. They take the forms of headache, and neuritic pains of " fibrositis " type. In some cases the adipose masses, often encapsulated, are very painful. Adiposis of girdle localisation, painfulness, asthenia and psychic disturbances constitute " Dercum's disease," but it is a useless piece of pigeon-holing to separate this disease from the general frame of hypothalamopituitary obesity

The biochemical syndrome is dominated by water and salt retention.

Water retention is shown by oliguria but is elicited more precisely through Volhard's water test. The patient is given one quart of water to drink within an hour in the early morning, while fasting and after urinating. Urine is then voided at half-hourly intervals and measured. Normally the whole quantity is excreted in the course of four hours, the greater part during the first two hours. In pituitary obesity, as in severe cardiac insufficiency and nephrosis, excretion is diminished. The test can be carried out while the patient remains in bed but results are more distinct if he remains upright.

Salt retention is investigated by means of another test planned by Volhard. A standard diet is given until the amount of sodium chloride excreted becomes constant. Then 10 grams of salt are added to the dietary. Normally this should be secreted within 24 hours. In pituitary obesity only a small quantity is excreted.

Other metabolic findings are less characteristic. Basal metabolism is sometimes diminished but there are great discrepancies in this finding. The same applies to diminution of the specific dynamic action of food. Polyuria instead of oliguria is encountered in cases in which the postpituitary anti-diuretin system is involved.

Mild or moderate hypothalamo-pituitary obesity can be cured by modern methods of treatment. On the whole it is a chronic disease. It certainly shortens life through defective resistance to disease and frequently through circulatory disturbances.

Special forms. Special forms of diencephalo-pituitary obesity can be described on the basis of the localisation of adiposis. In one such form a low-segment distribution of fat is seen, fat localising from umbilicus downwards. This condition is related to lipodystrophia, in which fat disappears from the umbilicus upwards but is normal in quantity below the umbilicus. In a

higher degree of localisation fat accumulates in certain well demarcated regions of the body and may even constitute large fatty tumours, the rest of the body being emaciated. Diet has not a great effect on this adiposis but mental and physical rest improve it.

Therapeutics. The therapeutic requirements in this form of obesity are (*a*) psychotherapy and nervous medication; (*b*) special dietotherapy; (*c*) physical methods and medicines acting on hepatic function and metabolism; (*d*) endocrinotherapy.

(*a*) Psychotherapy and nervous medication constitute a special item in the treatment of hypothalamo-pituitary obesities, whereas in nutritional obesities they are not prominent except for regulation of appetite. By helping the patient to a right mental attitude the internist contributes to re-establishment of neuro-endocrine balance and thus to cure of the basic neuro-endocrine disturbance responsible for the obesity. These patients improve on mental rest and calm but are made fatter by agitation. I have seen ballet dancers increase in weight because of internal mental conflict and continue to increase in spite of starvation diets and appallingly strenuous exercise, but when placed at rest far from the turmoil of the theatre they lost weight. To psychotherapy nervous medication can be added in the form of cratægus tincture, passiflora or valerian.

(*b*) Dietotherapy follows the lines indicated for nutritional obesity but need not be so severe, as it does not play a preponderant role. The only special item is restriction of salt and water, which in this form of obesity must be severe.

(*c*) The most important physical methods are tepid douches, warm baths, foam baths and peat baths as applied in certain spas. These procedures promote general metabolic function, and Porges has shown intensified excretion of chlorides and nitrogen products after mud baths. They increase also the local reactivity of the tissues to hormones. Spas are useful on the lines given for nutritional obesities, although the nervous sedative action of spa treatment seems here the most important element. In these forms of obesity I have seen good results from high altitude resorts of the St. Moritz type.

(*d*) Endocrinotherapy plays a greater role than in nutritional obesity. The simplest method is administration of a combined thyroid-total pituitary medication, beginning for instance with capsules or tablets containing 0·02 thyroid and 0·10 total pituitary and progressing higher according to results. In certain hypothalamo-pituitary obesities of the climacteric œstrogens are used, but I have seen no definite results. Chorionic gonadotropins in injection are sometimes helpful, although except for the diuresis they provoke their mechanism of action is not known. In some cases posterior pituitary extract injections have proved effective. A safe start can be made with 5 units, reactions and effects needing careful watch.

Diuretics are sometimes important among other medicines, particularly mercurial diuretics, as retention of water can be high in hypothalamo-pituitary

obesity. Laxatives also are necessary when constipation occurs. Hepatic stimulants, although less important than in nutritional obesity, have a place in treatment of this form. Benzedrine acts in some cases through an obscure mechanism but demands great care in administration.

Differential Nosography.

Deep Constitutional Obesity. Essential deep constitutional obesity is determined by a genetic disturbance of the intracellular liposynthetic-lipolytic neutral fat enzymes of the adipose cells which effect retention of fat in these cells (lipophilia). The adipose tissue of these individuals is abnormal in that it tends to accumulate fat and to resist its mobilisation.

The abnormal genes may be transmitted to the cells of certain regions only, hence regional differences of lipophilia. In steatopygia a special gene can be carried by males and transmitted to their offspring but manifested only in their daughters, the gene finding only in females the special gene-complex structure which allows it to be manifested. (It is not a sex-linked gene in the sense, for example, of the hæmophilia gene.)

The lipophilic gene is often pleiomorphic, determining metabolic disturbances which give rise not only to obesity but also to other conditions. In Danforth's strain of obese mice a single dominant gene accounts both for the obesity and the yellow colour (pleiotropism). In man also the lipophilic obesity may be pleiotropic. For instance, the Laurence-Moon-Bardet disease is caused by a gene which determines obesity and concomitantly hypogenitalism, polydactyly, retinal degeneration and mental deficiency. Morgagni's syndrome (hyperostosis frontalis) also is caused, according to some authors, by one gene determining not only lipophilia obesity but also the concomitant manifestations hyperostosis frontalis and hypertrichosis.

Clinically, in obesities in which the genetic lipophilic factor predominates notably, hereditary elements are very distinct and the obesity occurs early in life. It is usually a regular obesity involving the whole adipose tissue, these patients showing no special deformity. Face, trunk and limbs are equally involved, but exceptions occur, *e.g.*, steatopygia. Nervous, digestive and circulatory symptoms are not marked, but certain manifestations point to disturbances in the genetic phase of the individual's development. These are the so-called "stigmata of degeneration." In other cases, where the lipophilic obesity gene determines other disturbances, the deep constitutional obesity becomes simply one element in the clinical picture of a more complex disease, Laurence-Moon-Bardet disease.

Such obesities are very tenacious and resist all treatment. Therapy, however, must be applied, on the lines indicated for nutritional obesity. As in practice there are no absolute genetic obesities, other factors always intervening in addition (particularly the nutritive factor) such treatment has a rational basis.

CHAPTER XLVII

DIABETES INSIPIDUS

This disease was introduced into nosography by J. P. Frank in 1794, when on the basis of Willis' discovery of the sweet taste of the urine of certain diabetics a distinction was made between diabetes mellitus and diabetes insipidus. A pituitary physiopathological basis was first accepted by Harvey Cushing in 1912, when he found posterior pituitary hyperfunction on the strength of Magnus and Schaefer's conception of the diuretic action of the posterior pituitary. Later, however, hypofunction of the posterior pituitary was accepted, particularly after van den Velden had demonstrated the action of pituitrin injections in 1913. However, through the work of Camus and Roussy beginning that same year the postpituitary was dethroned in favour of the hypothalamus. A synthesis of the postpituitary and hypothalamic views has been effected of recent years through the outstanding work of Ranson, Fischer, Ingram and Richter.

Physiopathology and Etiology. Diabetes insipidus results from rupture of balance between such water-metabolic hormonal regulators as the water-catabolic or diuretic factors (thyroxin and parathormone systems) and the water-anabolic or water-retaining antidiuretic system. The diuretic factors are centred in the antepituitary. The antidiuretic factor, antidiuretin, is centred in the post-pituitary. Balance is broken when the antidiuretic system is in hypofunction. Diabetes insipidus is thus essentially a hypo-antidiuretinism, the hyposthenic state of this system originating either in the glandular centre of the system, the posterior pituitary (primary pituitary diabetes insipidus) or in the diencephalic centre (cerebro-pituitary diabetes insipidus). This has been demonstrated experimentally by Fischer and his collaborators. As stated in the introduction, the hypothalamic origin of the antidiuretin system is the nucleus supraopticus. In this nucleus originate fibres constituting the tractus supraoptico-hypophysarius, and through the pituitary stalk they terminate in the posterior pituitary gland, where they enter into contact with the cells secreting antidiuretin. An experimental lesion of any part of this system determines diabetes insipidus. When the anti-diuretic system is destroyed the water-catabolic hormones centred in the antepituitary act unchecked and abundant diuresis occurs. Thus, besides hypofunction of the post-pituitary anti-diuretic system, an essential condition for production of diabetes insipidus is the integrity of the diuretic systems centred in the anterior pituitary. When these systems are also in hypofunction diabetes insipidus does not occur.

Rupture of the balance between the diuretic and antidiuretic hormonal systems causing predominance of diuretic hormones leads to easy separation of water from the tissues and thus increased diuresis. Chloride metabolism, however, also is disturbed, although there are no definite data on this point. There are cases of diabetes insipidus with hyperchloræmia, others with hypochloræmia.

This is, I think, the safest physiopathological conception based on the precise experimental work of Fischer, Ingram and Richter, of diabetes insipidus, but is not accepted by all. Some authors hold, with Sato and Tredelenburg, that certain hypothalamic cells secrete antidiuretic hormone and thus the antidiuretinism of diabetes insipidus is centred in the hypothalamus. The arguments of these authors are not convincing in the light of modern research. Other authors maintain that diabetes insipidus is primarily a disease of the thirst centre of the hypothalamus, the polyuria resulting from the excessive consumption of water due to the increased thirst arising from disturbance of this centre. A disease of the thirst centre, a primary hypothalamic polydipsia, does in fact exist. It has been noted after certain interventions on the diencephalon (Bloch, Lhermitte and Abessard, Alajouanine) but it differs from diabetes insipidus. Excessive thirst comes first. Diabetes insipidus may follow and persist. It is possible that after involvement of the thirst centre the lesion progresses towards the supraopticus nucleus, but this primary hypothalamic polydipsia seems a separate disease.

The etiological factors causing the hypo-antidiuretinism responsible for diabetes insipidus may involve either the glandular or the cerebral centre of the anti-diuretin system.

Cases in which the glandular centre is involved, *i.e.,* cases of primary pituitary diabetes insipidus, are rare. However, tumours localised on the pituitary and destroying this gland without hypothalamic involvement have been noted. Simmonds reported a case of diabetes insipidus from a metastatic carcinoma of the posterior pituitary which left the pars intermedia and anterior lobe intact, Berblinger a case in which the pars intermedia was infiltrated with little colloid and the posterior lobe with sarcomatous material. Von Gierke reported cases of metastatic carcinoma of the posterior lobe, Sekiguchi a similar case free from any changes of the diencephalon. Maranon has collected cases of inflammation involving solely the posterior lobe and thus causing a primary infective pituitary diabetes insipidus, and Goldzieher has described a case in which there was cystic degeneration of syphilitic origin of the pars intermedia, extending to the posterior lobe, the anterior lobe being intact, and the resulting condition being therefore a primary pituitary diabetes insipidus through an inflammatory tumour.

The cerebral centre of the antidiuretin system is more frequently involved. A basic predisposing condition seems to be a genogenic inferiority of the antidiuretin system, which explains the hereditary and familial nature of the disease so well illustrated by Veil, who found 30 of the 220 members of five generations of a family afflicted with this disease.

The environmental factors which affect the diencephalic centre of the inferior antidiuretin system are (*a*) tumours pressing on the diencephalon, met in 63 per cent. of cases according to E. Frank; (*b*) infections localising on the hypothalamus or the basilar meninges, basal syphilitic meningitis being met in 13 per cent. of cases, tuberculous meningitis and tuberculoma in 6 per

cent.; (*c*) traumatic factors affecting the hypothalamo-hypophyseal region, as in the case of E. Frank, Berblinger, Kahler and Schumacher, and that of W. E. Dandy, in which surgical section of the pituitary stalk resulted in a diabetes insipidus of 11 years' duration.

Symptomatology. Onset is gradual. Progressively patients note that they void more urine and that they become more thirsty. There are exceptional cases of sudden onset after fright or emotion.

Polyuria is the dominating symptom. Patients urinate copiously day and night. 5–10 litres, even 20 litres, are excreted in the 24 hours. Frequency of urination coincides as there is so much urine to be excreted.

Polydipsia coincides. It may precede polyuria but usually follows it. The patient is thirsty and drinks abundantly because he loses much water. His life is spent passing from water-jug to urinal. If the intake of liquid is restricted, fever, nausea, vomiting, rigor, dyspnœa, tachycardia, and even death may occur. The patient cannot possibly restrict his water intake, and a patient of Streubell, when obliged to do so, did not hesitate to drink his own urine. Notwithstanding the high water intake the body becomes dehydrated, and in Aldrich McLure's test the liquid ingested is absorbed more rapidly than normally. The skin becomes dry and perspiration is inhibited.

Polyphagia is noted in some cases.

Such patients show, through concomitant hormonal disturbances, obesity, adiposogenital dystrophy, acromegaly and melanotic pigmentation.

The metabolic syndrome has not been fully established. The voided urine is of low specific gravity approaching that of water (1001–1005). The total quantity of its constituents (except of course of the water) is normal in a 24-hour collection. Thus urine is simply diluted. The blood chlorides are either increased or decreased.

Intracranial tumoral manifestations are encountered when the causal condition is an intracranial tumour.

The course of the disease depends on the etiology and is naturally much more severe in tumoral diabetes insipidus. On the whole it is a chronic and progressive condition, although remissions are noted, as during pregnancy (Duvoir, Polla and Cachin). Death occurs through an intercurrent infection or through the cachexia which follows the intense metabolic disturbances. Pituitrin controls diabetes insipidus as insulin controls diabetes mellitus.

Therapeutics. Etiological treatment should be attempted first. It is effective in cases of tumour and of syphilis.

Posterior pituitary extract is the basic procedure. It can be given in injection or inhalation (dry snuff method with post-pituitary powder).

Œstrogenic hormones in high doses may be used as adjuvants for women. They act by depressing the anterior pituitary. As diabetes insipidus results from posterior pituitary hypofunction, depression of the anterior pituitary, provided it is intact and thus able to exert its diuretic action, palliates diabetes

insipidus. When the disease is due to tumour, polyuria decreases when the tumour invades the anterior pituitary.

Restriction of the salt intake has been advised. Thyroideclomy, in my opinion, should be performed only exceptionally.

CHAPTER XLVIII

PINEAL MALE PUBERTAS PRÆCOX

This is due to a pineal tumour, usually a teratoma. Pineal tumours are rare, amounting to 3 per cent. of cases of intracranial tumour seen by Cushing and those associated with pubertas præcox are exceptional.

The mechanism through which a pineal tumour causes pubertas præcox is not known. Those who reject an endocrine function of the pineal consider that these tumours act by pressing on the hypothalamus, and according to them male pineal pubertas præcox would originate through the mechanism of a cerebro-pituitary hypercorticogenitalism or hypertestosteronism. Marburg holds that the pineal tumour determines pubertas præcox by destroying the pineal sex-inhibiting function. This is the most rational conception, but Boehm noted in a case of pubertas præcox a teratoma of the pineal, with large cells resembling the interstitial cells of the testis, which thus indicates another mechanism.

Pubertas præcox associated with pineal tumour has been described only in the male. The general picture is that of the complete adrenal form. Certain special characteristics, however, differentiate the intellectual syndrome and the intracranial symptomatology of the pineal disease.

These boys show an acceleration of mental development in contrast to the average or subnormal standards of the adrenal forms. In Frankl Hochwart's case a boy aged $5\frac{1}{2}$ with pineal tumour but a physical development of 15 years "spent much time in discussing the immortality of the soul and life after death." Psychological disturbances have been described but it is not certain whether they are due to the hormonal disturbance or the intracranial hypertension.

In the particular symptomatology of pineal tumours an outstanding place is taken by impairment or skew deviation of the upward gaze. As the tumour increases in size it presses on the aqueduct, and an internal hydrocephalus develops. Next, the nuclei of the third nerves situated in the periaqueductal region are involved. With further growth of the tumour the midbrain is compressed together with the pyramidal tract, the red nucleus, the cerebellar peduncles, and different forms of paralytic and ataxic gait become evident.

Treatment is of course surgical, when this is possible. The surgery of the pineal gland has been reviewed recently by Cecil Wakeley.

DISEASES OF THE PANCREAS-LIVER GROUP

CHAPTER XLIX

PANCREATIC OR HYPO-INSULINIC DIABETES

PHYSIOPATHOLOGY AND ETIOLOGY

Diabetes mellitus is an endocrine disease centred on disturbance of the carbohydrate metabolism but with widespread changes in body chemistry causing notable organic repercussions.

It was first described in the first century A.D. by Aretaios, who delineated the clinical syndrome, emphasised the polyuria and introduced the term diabetes. In 1674, Thomas Willis described the sweet taste of diabetic urine, which in 1776, Matthew Dobson, of Liverpool, showed to be due to sugar. On the basis of this work J. P. Frank, in 1792, divided diabetes into mellitus, *i.e.*, with sweet urine, and insipidus. Since then physiopathological research has shown that diabetes is an endocrine disease.

It was Thomas Cawley who, in 1798, first linked certain diabetes with pancreatic lesions, a view elaborated by the anatomo-clinicians Richard Bright (1831), Bouchardat (1851), Lancereaux (1877), and others, and confirmed by the experimental production of diabetes through pancreatectomy by Mering and Minkowski in Naunyn's laboratory in 1889. Establishment of the pancreas as an endocrine organ, mainly by Hedon and Laguesse in 1893, and principally the discovery of insulin by Banting and Best in 1921, proved conclusively the existence of pancreatic diabetes.

Hypo-insulinic or pancreatic diabetes is determined by deficient insulin secretion by the pancreas. A rupture then occurs in the neuro-hormonal regulation of carbohydrate metabolism. This regulation is effected by the hormonal systems which stimulate the liver to form sugar and inhibit sugar oxidation in the periphery (diabetogenin, cortin, adrenalin, thyroxin and sympathetico-hepatic systems) and by that which inhibits sugar formation in the liver and stimulates sugar oxidation in the periphery (insulin system). It is to be remarked that within this regulation of carbohydrate metabolism one system alone, the insulin system, balances a great number of antagonistic hormonal systems. This shows the great importance of a disturbance of the insulin system in the production of diabetes mellitus.

The hypo-insulinism responsible for pancreatic diabetes originates either in the pancreatic or in the cerebral centre of the insulin system. It may thus be a pancreatic or a cerebro-pancreatic hypo-insulinism.

Primary pancreatic hypo-insulinism arises from infections and intoxications affecting the pancreas directly, thus through the mechanism of pancreatitis. Such pancreatotropic infections as mumps are considered to be frequently responsible. Syphilitic pancreatitis also plays a certain role. Chronic pancreatitis often depends on an extension of a biliary tract infection to the pancreatic ducts, and thus cholecystitis and cholangiitis are often found in the history of such diabetics. Chronic pancreatitis develops slowly, hence diabetes may appear months or even years after the original infection. Recent work on the production of diabetes through pancreatitis localised in the islets of Langerhans and resulting from administration of alloxan (a bye-product of uric acid metabolism) points to the possibility of abnormal metabolites determining pancreatic hypo-insulinism.

Cerebro-pancreatic hypo-insulinism has a more complex and obscure etiology. A genogenic inferiority of the vago-insulin system is a basic factor of predisposition, and explains the very distinct familial and hereditary incidence of the disease. Of environmental factors affecting the diencephalic centre of the vago-insulin system infections probably play a certain role through the mechanism of encephalitis. Psychogenic factors loom large in the etiology of this form. Through cortico-diencephalic connections they upset the diencephalic centre of the vago-insulin system. This explains the frequency of diabetes in those belonging to professions demanding considerable mental strain.

Dietetic factors are very much discussed. Like all the etiological factors in diabetes, they participate within the frame of a constellation of etiological conditions. Many doubt whether excessive consumption of sugar is important in the genesis of this disease, some authors, like Himsworth, even believing that diabetes can be provoked by a diet deficient in sugar. However, any alimentary load, particularly of carbohydrate nature, strains the neuro-hormonal systems regulating carbohydrate metabolism and may thus induce a definite disturbance.

Meteorological factors have lately been stressed by W. F. Petersen, who holds that, given a suitable constitution and the hereditary background, the variable environment of the cyclonic tracks makes manifest metabolic deficiencies which under other conditions would remain adequate for normal needs. He demonstrated this by many observations. In very changeable climates people live more actively and thus make greater demands on their autonomic nervous systems, and the continuous adaptation to changes of temperature has the same effect. All this upsets the neuro-hormonal systems regulating carbohydrate metabolism. For this reason, diabetes is more frequent in such climates and its clinical course deteriorates with weather variability. The insulin system becomes inadequate to meet the level of activity demanded by

the high metabolic requirements of a vigorous life. Diabetes mortality has been shown to be related to climatic stimulation, the disease becoming a major medical problem in regions of invigorating climates. Diabetics from the north improve on migrating to the south, and diabetics migrating from the south to thr north are aggravated.

Trauma also has been noted as an etiological factor. Trauma of the pancreas cannot produce true diabetes as it is never sufficiently extensive (the experimental production of diabetes necessitates the almost complete removal of the pancreas). Organic injuries to the central nervous system are more important.

Exceptional factors may exist, *e.g.* tumours pressing on the diencephalon (Nonne, Oppenheim). Obesity and arteriosclerosis are not "causes" of diabetes. They are concomitant manifestations, due to the same factors that upset the insulin and other neuro-hormonal systems regulating carbohydrate metabolism. Possibly, however, some of the diabetogenic factors act through the mechanism of arteriosclerosis of the pancreatic vessels.

All these factors act in combination. There is no one "cause" of diabetes, but only etiological conditions. It is for the endocrinologist to determine in each individual case the respective roles of these factors and their mode of combination.

The Metabolic Disturbances. The basic metabolic disturbance bears on *carbohydrate metabolism*. When insulin, the stimulant of glycogen storage and sugar oxidation, is deficient the contra-insulin hormones are unchecked. Glycogenolysis, *i.e.*, sugar production by the liver, becomes excessive and carbohydrate oxidation in the muscles and other tissues diminishes. Sugar thus accumulates in the blood (hyperglycæmia) and is excreted in excess in the urine (glycosuria). Sugar is a threshold substance, and when it rises above its threshold in the blood it passes into the urine. Through the preponderant action of glycogenolytic processes the remaining liver glycogen diminishes and its formation after administration of sugar is decreased. Muscular reserves of glycogen also diminish but for some unknown reason the glycogen content of the heart muscles is increased. The unchecked anti-insulin hormones inhibit peripheral tissue oxidation of sugar. This is diminished but not abolished in pancreatic diabetes, as shown by the study of the respiratory quotient and other experimental studies.

Protein metabolism also is disturbed, protein catabolism being intensified. The main action of the principal anti-insulin hormone, pituitary diabetogenin, is to produce sugar from proteins (gluconeogenesis), and when it acts unchecked gluconeogenesis is intensified. Thus much of the protein ingested with food, instead of serving to build up cellular material, is used to make carbohydrate. Further, the diabetic organism failing to burn carbohydrate to obtain the necessary energy, burns much of the protein that should be used for the same purpose of building up cellular material, and ultimately that of its own cells. All this causes the intense denutrition of the diabetic and his negative nitrogen balance.

Disturbance of fat metabolism is very important. Certain lipids such as cholesterol accumulate in blood, probably through coincident deficiency of the fat-metabolic factor of the pancreas or pituitary.

Lipids in general and neutral fats in particular are imperfectly catabolised, *i.e.*, oxidised, and this defective oxidation gives rise to ketone bodies which accumulate in the blood and are like the soot from a smoking lamp (Woodyeat). The precise cause of imperfect fat metabolism leading to acidosis is not known. Rosenfeld's phrase, that " fats burn in the flame of carbohydrates," and its corollary that imperfect carbohydrate burning in diabetes results in imperfect burning of fat, do not indicate a precise physiopathological mechanism. It is more probable that the unopposed fat-catabolic-inhibiting function of diabetogenin or a special ketogenic factor of the antepituitary are concerned.

Ketonic acids accumulate in the blood. The normal reaction of the body against the threat of acidification occur. The alkalies of the blood, CO_3 NaH in particular, are used to neutralise the acids, and thus the alkaline reserve dwindles. Expressed in carbon dioxide capacity of the plasma, the normal alkali reserve is 80–52 volumes per cent. In mild ketosis it is 53–40 per cent., in moderate ketosis 40–30 per cent., in severe cases below 30. Real acidification of the blood does not occur so long as the alkalies neutralise the acids. The " acidosis " in these cases is in fact a compensated acidosis, or more precisely a diminution of the alkali reserve. When this reserve is exhausted, however, or for any reason the buffer action of the body is in abeyance, true acidosis, *i.e.*, uncompensated acidosis of the blood occurs and the *p*H of the blood diminishes.

The compensation of acidosis, however, is more complex than simple neutralisation with CO_3 NaH. A compensatory hyperpnœa due to stimulation of the respiratory centre by the acidotic blood flowing through it leads to excessive loss of the acid CO_3H_2 through excessive loss of CO_2, which falls in tension in the arterial blood and thus in the alveolar air. Thus the acidity of the blood diminishes. More ammonia is produced by the renal cells, and this also serves to neutralise the ketonic acids formed, and finally the kidney exerts itself in excreting the acids accumulating in the blood.

Water excretion rises and polyuria results. Owing to hyperglycæmia glucose is not completely reabsorbed in the renal tubules in the normal manner, and sugar is highly concentrated in the glomerular filtrate. This increases the osmotic pressure, absorption of the usual quantity of water is inhibited, and polyuria is the consequence. The excessive water loss causes an increase of thirst.

Other biochemical processes of the body are disturbed, the details of these disturbances being impossible, however, in a work of this nature. There is need for a comprehensive and synthetic work giving exact details of the disturbances of body chemistry in diabetes.

These important changes in body chemistry result in widespread disturbances of the functions of the body-mind and the state of the organs. Normal composition of the internal environment is necessary for free life, but is

seriously modified in the diabetic. Cellular functions for growth are in abeyance. Cellular functions for production of antibodies also are impaired, hence lowered resistance to infections and other physical and mental insults. Life flows at a low ebb in the untreated diabetic. He cannot adapt himself to environment and becomes a fragile vessel. A whole series of manifestations due to lack of resistance to infections occurs. Disturbance in cholesterol metabolism gives rise to various cardiovascular manifestations. The changes in the blood flowing through the nervous system impede the functions of the nerve cells, which are essentially sensitive to changes of internal environment. When acidosis occurs cellular functions are even more grossly impaired, particularly those involving the nervous system. Of all the internal environmental changes the alteration in *p*H is that which the cells resist least. All these organic repercussions will be studied in more detail in the clinical history.

Symptomatology.

The Common Form. Mode of Onset. Pancreatic diabetes develops very slowly, and in its beginnings is often very difficult to diagnose. Lasègue used to complain that no accurate history of the mode of onset of diabetes existed, and since his time nothing of great importance has been added to that chapter despite the legacy from Sir James Mackenzie of a more accurate examination of symptoms.

The carbohydrate metabolic disturbances, like all metabolic disturbances, are manifested at first by certain general symptoms, which include fatigue, malaise, headache, disturbance of appetite. All these symptoms are vague and have not yet been accurately tabulated. Many diabetics begin their disease in the form of a simple neurasthenia, and the routine examination for sugar in the urine directs diagnosis.

In other cases there are definite symptoms and organic localisations. Patients come with furunculosis, or because they have a bad taste in the mouth, or because they experience excessive thirst or appetite, or for progressive loss of weight. Some patients consult the physician in the first place for various cardiovascular disturbances, and again the routine examination for urinary sugar includes them as pancreatic diabetics.

There are exceptional cases in which the diabetes has hitherto escaped diagnosis, and the first clinical manifestation is coma. Many years ago Brouardel emphasised the fact that many sudden or rapid deaths requiring medico-legal opinion were due to diabetic coma.

In the vast majority of cases, however, no symptom points distinctly to any illness. In the course of routine health examination or insurance examinations the diabetes is discovered through urinary tests. Such cases are so frequent that the urine of every patient should be tested for sugar as well as for albumen.

When diabetes occurs early in life it retards development of the child, particularly physical development. The result is pancreatic infantilism constituted of maldevelopment of stature, disturbed development of the genital organs, and up to a certain point disturbed mental development. These points,

however, are somewhat theoretical, because before the advent of insulin child diabetics usually died, and since the use of insulin such disturbances are not found, or if found, are very slight.

General clinical picture. The habitus of diabetics varies. In many cases weight is normal. In severe untreated cases loss of weight is marked. In some cases obesity develops, probably through involvement of the fat-metabolic function of the pancreas and over-nutrition. Fat diabetics run a milder course.

Symptoms referring to reactivity are outstanding. Asthenia is constant. It is the symptom which leads many diabetics to medical consultation and discovery of their disease, and has often misdirected diagnosis to " neurasthenia." Polydipsia and polyphagia, often for starchy foods in particular, are very frequent. Resistance to infections, especially to pneumonia, is poor, but strengthened to-day by insulin administration. In pre-insulin days diabetics often died from mild infections, trauma or even a minor operation.

Hypogenitalism is marked. Impotence and absence of libido are among the first symptoms in men. In women oligomenorrhœa and amenorrhœa are common, and incipient diabetes is to be considered in women consulting for these menstrual disturbances. Fertility is very low in both men and women. Von Noorden noted only nine pregnancies in 240 women between 20 and 40 after the onset of diabetes.

Psychological features are not very characteristic. Loss of memory and lack of concentration may be presenting symptoms, however, for which diabetics seek advice without knowing of their disease. I have often noted in my diabetic patients an unaccountable depression and sadness at onset.

The organic symptomatology is very rich, although the severe organ localisations of pre-insulin times are not seen to-day.

Neuralgia and neuritis are among the most frequent, and diabetes is often found in patients consulting for double sciatica. Neuritis can develop as polyneuritis with ataxic symptoms and absence of patellar reflexes (diabetic pseudotabes). In all these cases vitamin B deficiency intervenes. Cataract and retinitis are outstanding ocular manifestations. Cerebral symptoms result from diabetic cerebral atherosclerosis.

Atherosclerotic manifestations are of great importance. They arise from disturbances of cholesterol metabolism due to dysfunction of the fat-metabolic factor of the pancreas. They occur frequently nowadays, because on insulin diabetics live long and insulin does not neutralise the disturbance of pancreatic lipid metabolic hormone. The localisation of atherosclerosis varies, but cerebral and coronary atherosclerosis and " endarteritis " obliterans of the extremities are often seen. Coronary atherosclerosis with its manifestations of angina pectoris and coronary thrombosis is the most frequent localisation, Nathanson finding it in 52 per cent. of diabetics over 50 years of age against 8 per cent. in non-diabetic controls. In diabetics with coronary atherosclerosis a sudden hypoglycæmia, due for instance to insulin overdosage, can provoke attacks of angina and coronary thrombosis.

Stomatitis and cholecystitis are the most important digestive manifesta-

tions. Stomatitis and gingivitis arise from infections which prevail against the low resistance of diabetics. Cholecystitis is found in 10–24 per cent. of cases and is explained by the coincidence of pancreatitis or by disturbances in cholesterol metabolism. Cholecystectomy presents grave danger to the diabetic, and even after successful operations adhesions are formed with painful syndromes as an aftermath.

To sum up, many forms of organic disturbances are noted in diabetics. Those described above are mainly due to the metabolic disturbances characterising this disease. Another group showing great variety is constituted by infections acting on these poorly resistant individuals. The stomatitis already described, respiratory infective manifestations, acute and chronic, such as tuberculosis, skin infections, boils (frequently a presenting symptom), eczema, urinary infections, liability to which should always be considered in diabetics needing catheterisation—all these infective processes in diabetics may easily be overlooked because they develop silently.

Biochemical symptoms. The important biochemical symptoms are glycosuria, hyperglycæmia and a special blood sugar curve in the glucose tolerance test.

Glycosuria is assessed approximately by the Benedict qualitative test but more precise quantitative methods are usually necessary. Figures as high as 10 per cent. can be found, the average being 5 per cent. The total excretion of sugar per 24 hours varies from a few grams to 100 grams and more.

Hyperglycæmia is of greater significance. With the Folin-Wu method or its derivatives the normal range of blood sugar is 90–120 mg. per cent. In mild diabetes values of 140–300 mg. exist, and in severe diabetes values up to 1,200 mg. The normal threshold for blood glucose is 160–180 mg. per 100 c.c. Above this level glucose " spills over " into the urine. In diabetes the threshold is frequently raised and for this reason sole reliance should not be placed on urinary determinations.

The special response of blood sugar to glucose tolerance test is the blood sugar curve after ingestion of a certain quantity (50 grams, or 1 gram per kilo of weight). Three or four specimens at hourly intervals are collected and analysed for sugar. In normal subjects the blood sugar rises from the normal value of about 100 mg. per cent. to 150 at the end of an hour and returns to normal at the end of the second hour. In pancreatic diabetes the quantity at the end of an hour is over 150 milligrams and continues high at the end of another hour. It is unnecessary to use this test if the blood sugar is high from onset.

There are signs of disturbance of other metabolisms. Increase of urinary nitrogen indicates intensive protein metabolism. Imperfect utilisation of lipoids is shown by increase of cholesterol in the blood, in which values up to 600 milligrams per cent. are found instead of the normal 110 to 190.

Course of the disease. Some cases of pancreatic diabetes are cured either spontaneously or more frequently by treatment. Many such patients are maintained in perfect health by occasional visits to spas.

In other cases the disease lasts throughout life but is perfectly controlled by insulin. The subject can be considered normal and on the whole his life is not shortened. He dies at an advanced age, usually from cardiovascular disease, which often develops in diabetics even when their disease is under perfect control.

In a third class, diabetics, even when under insulin control, die before their time of an intercurrent infection (pneumonia) or an operatory shock. They are not sturdy subjects.

Finally, a certain group of diabetics develop acidosis, which is described in a separate chapter.

Diagnostic leaders. Diagnosis is relatively easy for those who make a routine examination of the urine and remember diabetes in states of fatigue, " neurasthenic syndrome," polyphagia and polydipsia, loss of weight and the other clinical syndromes delineated in the symptomatology.

Renal glycosuria may be a stumbling-block. In this disease, probably on the basis of disturbance in the neuro-vegetative regulation of the kidney glucose excretion function, the kidney does not retain sugar. The threshold for excretion of sugar is lowered. The disease is benign, shows no hyperglycæmia, and gives a special curve on glucose tolerance test.

Certain benign and transitory glycosurias enter into consideration. They are in fact conditions of diabetes, but mild and temporary. The same rupture of balance in carbohydrate metabolic regulation occurs but does not persist. These states develop in the course of certain infectious diseases, states of mental tension, dietetic upsets and intoxications. The benign and passing character of the condition and the existence of symptoms of another morbid condition help diagnosis.

Certain melliturias other than glycosuria also need to be considered. The basic diagnostic measure is determination of the form of the urinary sugar. Such conditions are benign. Essential levulosuria is one of them. It is rare and something of a clinical curiosity. Alimentary levulosuria occurs in individuals with hepatic insufficiency. Essential pentosuria is to be considered on the same lines. Lactosuria occurs in women during lactation. Galactosuria is seen in nursing.

The Acidotic Form (Diabetic Acidosis). Diabetic acidosis is a terminal syndrome of certain hypo-insulinic diabetes. A diabetic becomes acidotic because of inadequate treatment, physical and mental strain, trauma or surgical intervention, infections and intoxications, principally after intoxication following surgical anæsthesia. All these factors, potent in the pre-insulin era, are less prominent to-day because insulin tides the diabetic over difficult episodes and helps him in particular to support infections and surgical interventions.

Diabetic acidosis occurs in the form of an acute attack, although its preparation may take some time. It falls into four phases, the latent, the prodromic, the pre-comatose and the comatose. An important biochemical

syndrome is common to all these clinical stages.

In *the latent phase* patients feel nothing of note, but a routine urinary examination shows ketone bodies. This latent phase may be very prolonged. In pre-insulin days in particular, many authors observed that diabetics with urinary acetone but without symptoms could last a long time without entering into the more severe dyspnœic-comatose or comatose collapse form. This is not the rule, however, and discovery of acetone should lead to intensive treatment.

The prodromic phase is important because if it is detected, early and successful treatment can be instituted. Its symptoms are far from clear, and it is safe to regard any deviation from the normal occurrences in a diabetic as premonitory of acidosis. In general the patient experiences headaches, general malaise, listlessness or nervousness. He feels more tired than usual—a very early symptom—and sometimes slightly drowsy. He has pains in the back, a heavy and coated tongue, and is sometimes mildly nauseated.

The pre-comatose or dyspnœic phase follows quite soon. It is characterised by general symptoms, dyspnœa, cardiovascular collapse and digestive disturbances.

The general symptoms are those of the prodromic phase intensified. The patient looks very pale. Malaise, nervousness and irritability are evident. Alternating with these and sometimes dominating them, drowsiness is noted.

Dyspnœa is the outstanding symptom, and has caused this phase to be known as the dyspnœic phase. It may be of ordinary type with oppression and tachypnœa but in most cases is of characteristic Kussmaul type. The patient complains of severe oppression, but air seems to enter and leave the lungs without the slightest obstacle. The respiratory movements are accelerated but strong, and the contrast between the general weakness and the intense respiratory processes is one of the most marked features of the state. The thorax dilates in all directions. Complete inspirations are followed by complete expirations. The veins of the neck show no blood stasis and the accessory respiratory muscles no evidence of effort. Notwithstanding this there is gasping and air hunger. Fruity odour of the breath in some cases completes the respiratory syndrome.

Circulatory collapse also is pronounced. It is a peripheral collapse. The pulse is fast and may reach 140 but in some cases is slow. However, whether fast or slow it is barely perceptible and blood pressure is very low.

Digestive upsets appear as nausea, vomiting, abdominal pain. In some cases they constitute a real symptom complex of acute abdomen, with intense abdominal pain, local or general, resistance of the muscular wall and abundant vomiting. The acute acidotic abdomen raises the important diagnostic problems. Practically, however, whenever a patient with acute abdomen shows acetone in the urine the first step should be treatment of the acidosis. When this has cleared, and if the acute abdominal state has disappeared simultaneously, a metabolic acidotic origin is indicated. If it does not clear an intra-abdominal condition should be sought and treated, operation being fairly safe as acidosis has disappeared.

Phase of coma. Some patients recover after the prodromic or the dyspnœic-digestive phase. Others pass into the terminal or comatose phase. This phase may even be the first manifestation of acidosis or even of diabetes. Patients without notable symptoms and even without acetone in the urine collapse suddenly into deep coma with grave cardiovascular symptoms. Death may occur suddenly in the street and raise medico-legal problems.

Usually from simple drowsiness the patient slips progressively into profound coma, which frequently arrives very soon. He often moans as though in pain. The skin is dry and cold, the face flushed and drawn, and tissues are obviously dehydrated. The eyeballs are soft, an important sign of ocular hypotension. The mouth is dry, the tongue dry and coated. At intervals dark brown material, obviously changed blood, is vomited. On being turned or examined the patient cries out as if in pain. Abdominal findings frequently resemble those of the previous phase. The pulse is very rapid. The temperature is usually low or normal, but rises if infection is present. The blood pressure is low. The muscles are flaccid, tendon reflexes diminished or absent, and pupils dilated. A drop of adrenalin applied to the eye causes notable dilatation of the pupil (Loewy reaction). Dyspnœa exists, but is usually of stronger form than the Kussnaul type.

Untreated patients always die after reaching this stage. Those treated with insulin may recover, but even with insulin death is frequent. Older people in particular and those with cardiocirculatory disturbances derive less benefit from insulin in this respect. Severe acidosis and prolonged unconsciousness prior to administration of insulin are other factors that, in spite of insulin, make for death. These and transformation of Kussmaul dyspnœa into feeble and gasping breathing are of bad prognosis.

The entire picture of diabetic acidosis is complex and aggravated in some cases by a concomitant cardiovascular disease leading to cardiac insufficiency, a concomitant nephritis leading to uræmia or a cerebral hæmorrhage. Detection of these associated conditions, so important in therapeutics and diagnosis, taxes the diagnostic powers of the internist.

Biochemical syndrome. This is encountered in all phases of diabetic acidosis. The following essential characteristics indicate acidosis but not necessarily a diabetic acidosis.

1. Presence of acetone bodies in the urine (diacetic acid, acetone, β-oxybutyric acid).

Acetone and diacetic acid are found in normal urine to the extent of 3 to 15 milligrams per diem, β-oxybutyric acid ranging from 20 to 30 milligrams per diem. In diabetes, 0·02 to 6 grams of combined acetone and diacetic acid are found, and 50 to 100 grams or more of β-oxybutyric acid.

2. Diminution of the alkaline reserve of the blood. This can be assessed by Van Slyke's carbon dioxide capacity of the plasma. The normal is 65 volumes per cent. of carbon dioxide, in diabetes values ranging from 53 in mild acidosis to under 30 in very severe acidosis are found. It can be estimated also by Fridericia's alveolar carbon dioxide tension. The normal is

5·5 volumes per cent. of carbon dioxide. In diabetic acidosis the value falls as low as 2 per cent.

3. Disturbances of the alkali tolerance. This is a less characteristic sign. Normally the administration of 5 to 10 grams of bicarbonate is sufficient to produce an alkaline reaction in the urine. In diabetic acidosis a greater amount is required, but much depends on the capacity of the kidneys to excrete alkalies.

4. Increase of blood *p*H. This is detected by such procedures as Hawkins' modification of Cullen's colorimetric method. The normal *p*H of blood is between 7·3 and 7·5. In severe acidosis the extreme limits of 6·95 and 6·8 are reached.

Diagnostic Leaders.

Few problems in internal medicine are as urgent as the accurate diagnosis of diabetes with acidosis, particularly in the pre-comatose and comatose stages. Error may be fatal, while a correct and early diagnosis has proved life-saving. The problem is essentially clinical, for there is no time for any laboratory procedure more complicated than urine examination.

Knowledge of the history of the patient is extremely useful. If the physician has had for some time under his care the diabetic who progresses into acidosis, diagnosis of the pre-comatose stages, described as the first and second phases, is relatively easy. Any out-of-the-ordinary symptom, as has been pointed out, must be considered indicative of acidosis.

In these first two phases the patient can pass urine, and rapid examination with ferric chloride (which should always be in the bag of the physician) enables him to make this diagnosis. When the patient is already in coma when seen, and particularly when the history is not known, difficulties are very great. The patient passes no urine, but if possible a catheter specimen should be obtained and examined for acetone bodies. In such cases there is no time to wait for blood examination, but this should be done as soon as possible.

Haste is important, for treatment is effective only if it is applied early enough. It is one of the cases to which can be applied the words of Napoleon: "In great battles it is the quarter-hours that count."

Differential diagnosis is made, first, from hypoglycæmia due to insulin. Diagnosis is helped by the following table of comparison.

Etiological Syndrome.

Acidosis.	*Hypoglycæmia.*
Too little insulin.	Too much insulin.
Too much food.	Too little food.
Presence of infection usual.	No infection present.

General Symptoms.

Restlessness.	Apathy.
Distress gradually approaching unconsciousness.	Irritability. Hysterical manifestations gradually approaching unconsciousness. Child becomes

	quiet, lacks interest and is unnaturally good. Adult becomes depressed.
Gradual improvement within an hour with insulin.	Sudden improvement within a few minutes with carbohydrates by mouth, by rectum, intravenously or subcutaneously.
General appearance florid, extremely ill.	Appearance pale, weak, faint. Sudden onset of symptoms.
Fever frequent.	No fever.
Skin dry.	Skin moist.
Hunger absent, thirst extreme.	Hunger frequent and extreme, no thirst.
Urinary sugar present.	Urinary sugar absent, or invariably absent in the second of two specimens.
Gradual improvement with carbohydrate administration.	Sudden improvement with carbohydrate administration.

Organ Symptoms.

Tremor absent.	Tremor frequent.
Vision dim.	Vision double.
Respiration exaggerated (air hunger).	Respiration normal.
Vomiting common.	Vomiting rare.
Abdominal pain frequent.	No abdominal pain.
All symptoms improve in time with insulin but are aggravated by carbohydrates without insulin.	All symptoms improve with carbohydrates by mouth, by rectum, intravenously or subcutaneously.

The differentiation of hypoglycæmic coma due to overdosage of insulin from diabetes with acidosis has been outlined in detail because it is one of the most serious problems of practice. In doubtful cases sugar should be given. If the coma is due to overdosage of insulin and consequent hypoglycæmia, symptoms are relieved rapidly. If the coma is due to acidosis relief is obtained but is less marked. Before proceeding further, however, diagnosis must be more exact, for if in a case of hypoglycæmic shock insulin is given in the strong doses necessary for diabetes with acidosis, the patient may die.

Coma due to cerebral lesion is differentiated mainly through the symptoms of involvement of cerebral localisation such as unilateral paralysis, inequality of the pupils, puffing of one cheek more than the other during exhalation, inequality of reflexes. The breathing in such cases is not of Kussmaul type but is a special stertorous dyspnœa. The biochemical findings of course fix the diagnosis.

Coma due to poisoning is differentiated by the clinical history and by some

peculiarities of intoxication such as the pin-point pupils of opium intoxication and the bright cherry red colour of the blood in carbon monoxide poisoning. Here also the biochemical signs are the leaders.

Uræmic coma is one of the most difficult problems of clinical differentiation. The Cheyne-Stokes type of dyspnœa favours a diagnosis of uræmia. The biochemical symptoms are essentially diagnostic, but it should be remembered that certain diabetics show high blood nitrogen due to renal complications.

Combined forms must be considered, and it should not be forgotten that a diabetic can enter into non-diabetic coma.

The Diabetoid Form (Forme Fruste). Like all other endocrine diseases, pancreatic diabetes appears as formes frustes. These can be designated diabetoid. It is produced by a mechanism absolutely similar to that of common form but much milder. The conception of this forme fruste is of great help in clarifying clinical work, obviating the unnecessary distinction between "diabetes" and "temporary glycosuria," for instance, a distinction justified symptomatologically but not physiopathologically.

The clinical manifestations of diabetoid are: (*a*) Temporary benign glycosuria. A small quantity of sugar is found in the urine, often intermittently and only for a short time. This glycosuria often appears after meals. (*b*) Alimentary glycosuria, known also as carbohydrate intolerance. Glycosuria occurs after ingestion of 50 grams of glucose, a quantity with which a normal person deals adequately. (*c*) Diabetic curve on glucose tolerance test, more or less marked, but no fasting hyperglycæmia.

Any of these symptoms can exist alone. Diabetoid can disappear or pass into the common form of diabetes.

The etiology of pancreatic diabetoid is that of pancreatic diabetes in general, but is frequently encountered in the course of certain infections and during emotional upsets, often as the monosymptomatic manifestation of temporary benign glycosuria.

Special Forms.

Diabetes of Children. In the United States 5 per cent. of diabetics are children. The frequency of diabetes increases from birth to the 12th year and decreases between the 12th and 16th years. It is thus most frequent towards puberty in relation to the endocrine storm of that phase of life. Juvenile diabetes is particularly common among Jewish childrern.

It is probable that the majority of infantile and juvenile diabetes are not pancreatic, *i.e.*, hypo-insulinic, but pituitary. This conclusion has been drawn by many authors, especially by P. White, from the presence of symptoms indicating pituitary hyperfunction—spurt in growth, at all events before the onset of diabetes, advanced bone and dental development, elevated basal metabolism and precocious puberty.

In the etiological constellation infections are common. A hereditary element is more frequently apparent than in the adult diabetic. The present-

ing symptoms are furunculosis and other skin infections, visual changes, pains in the muscles of the extremities, personality changes, lack of concentration on school work.

Once established the disease is manifested by a rich symptomatology. Polydipsia, polyphagia and cachexia are marked. Skin complications such as xanthosis are frequent. Premature arteriosclerosis and cataract are often seen. Dental caries and pyorrhœa are so marked that the dentist should suspect in such children an unrecognised diabetes. Hepatomegaly and splenomegaly are not uncommon. The precocious development of the child in the pre-diabetic period or at the onset of diabetes is followed by retarded development in the succeeding years. Staturally and sexually development is arrested.

Acidosis occurs as a rule in untreated patients. There are even cases in which acidosis is the first manifestation of diabetes.

The outlook was very grave in pre-insulin days but since Banting and Best's discovery prognosis is much more favourable.

The Symptomatic Diabetes. These are diabetes constituting part of the general clinical picture of certain clearly distinguished non-pancreatic endocrine diseases.

Diabetes, in complete or in its diabetoid form, occurs in pituitary acromegaly and pituitary gigantism. It is explained by an initial hypersecretion of pituitary diabetogenin which causes excessive glucogenesis and a secondary hypo-insulinism.

Diabetes or diabetoid occurs in Cushing's disease and in adrenocortical carcinoma. It is explained by hypersecretion of the sugar steroids of the adrenal cortex. Here also a secondary hypo-insulinism intervenes.

Diabetes or diabetoid occurs in adrenomedullary tumours and in Graves' disease. Here also the initial event is hypersecretion of adrenalin or thyrohormone, which are contra-insulin hormones.

Finally, diabetoid occurs in certain liver diseases involving the enzymes of the hepatic cells.

Other Endocrine Diabetes. On the basis of the metabolic regulation of carbohydrate metabolism diabetes can be pigeon-holed into pituitary, adrenal, thyroid and hepatic forms. In such cases the primary event is hypersecretion of one of the contra-insulin hormones.

In human biology, however, things are not so simple. Hypo-insulinism causes a hypersthenic reaction of the contra-insulin hormones, and vice versa. Endocrine diseases are not diseases of one endocrine gland, but rupture of the balance of hormones. Thus the unicist theory of diabetes is more in conformity with clinical conceptions. With these reserves, however, we can accept diabetes and diabetoids in which the initial event is hyperfunction of one of the contra-insulin hormones. These are cerebro-pituitary hypersecretion of pituitary diabetogenic hormone, cerebro-pituitary hypersecretion of the sugar steroids of the adrenal cortex, and diabetes determined initially by hyper-

function of the thyrohormone, sympathetico-adrenalin and sympathetico-hepatic systems.

Clinical differentiation is at present impossible. Clinical significance is nil, as all these forms enter into the general handling of pancreatic diabetes except that in diabetes in which the initial disturbance is hypersecretion of pituitary diabetogenin or of the adrenocortical sugar steroids, insulin resistance is encountered.

THERAPEUTICS.

Therapeutics of the Common Form of Diabetes. Therapeutics of hypo-insulinic diabetes is a matter of both principles and details. The details are extremely important but cannot be given in a work of this nature. The principles are given here to provide definite orientation in the complicated detailed technique indicated in standard works such as those of von Noorden, Falta, Joslin, Wilder and of Lawrence.

Diabetes is a constitutional disease and thus a "holistic" condition. For this reason its treatment cannot be summarised adequately in the words "diet and insulin" but requires application of the principles of modern constitutional medicine and therefore demands consideration of all general constitutional procedures.

Thus psychotherapy acquires great importance. I followed diabetics treated by a Paris clinician of great biochemical knowledge. His diets were carefully planned and dosage of insulin mathematically computed. But as this clinician had a deep contempt for all notions of psychogenic influence in disease and shunned any psychological investigation and treatment, his results were far below those of a colleague in the same hospital whose biochemical knowledge was elementary and who had to rely on his assistants for the application of insulin in the rare cases in which he dared to employ it. His therapeutic results were far superior to those of his learned rival because, as a truly Hippocratic physician, he could understand each patient as a whole and with his fine personality influence the shattered nervous system. It is not astonishing, therefore, that a biochemist even of the capacity of Woodyeat has said that in many cases of diabetes mellitus it is more important to follow the emotions than the blood sugar curve.

Regulation of the general health, simple on paper but demanding great clinical skill in practice, is equally significant. It must therefore be adapted to the dosage of insulin and regulated with care. Written instructions should be given. In some cases I have even been able to abolish insulin, prescribed after nursing-home observation, from the treatment of diabetics, by making them walk two or three miles a day in the open air. This daily walk has the effect of a small dose of insulin.

There is no doubt, however, that dietotherapy is a basic procedure. The mistakes made in the course of development of this procedure, however, show the dangers of considering one side of the problem and ignoring the whole constitution. It was easy to say that as fat does not produce sugar the diabetic should follow a diet in which the caloric needs were satisfied nearly exclusively

by fats. The result of these Petren diets was severe acidosis, indicating the difference between the complicated human constitution and the test tube. The Cantani high protein diet offered the same defect. It increased hyperglycæmia and glycosuria instead of diminishing them because the body is able to make sugar out of proteins. A similar error coloured the high carbohydrate diets favoured by recent authors on the basis of theoretical considerations. Even with the more scientific diets of to-day the need for individualisation is great. A normal person weighing 9 stone 6 lb. and taking moderate exercise needs proteins 60 grams, fats 60, carbohydrates 250. A diabetic of similar weight and habits needs, according to numerous treatises, proteins 75 grams, fats 90, carbohydrates 150. eHowever, these figures show discrepancies. As regards proteins, such a diabetic needs 40 grams according to Marsa Newburgh and his associates, 120 grams according to Porges and Adelsberg, 60–80 grams according to von Noorden and Joslin. As regards fats, some authors advise more than the 60 grams mentioned above, and there are similar discrepancies in the carbohydrate figures. The ketogenic anti-ketogenic ratios of many textbooks are also being abandoned.

All these discrepancies can easily be explained. Some diabetics tolerate a high protein diet but others need to be limited to the lower limits. Similar degrees of tolerance are found bearing on fats and carbohydrates. We return therefore to the essentially individualistic clinical empirical method which forms the basic procedure of endocrinology and constitutional medicine, and which in relation to diabetes includes laboratory procedures judged, however, in the light of the whole clinical picture.

For a diabetic weighing 9 stone 6 lb., therefore, the rough formula proteins 75 grams, fats 90, carbohydrates 250, can be maintained but needs modification according to his tolerance. The dietotherapy of diabetics must be computed not mathematically but with clinical vision.

An important point is the difference in the dietotherapy of fat and lean diabetics on which past medical generations, with less mathematics and more clinical vision, insisted. Fat diabetics must have a low calory diet and their weight must be reduced. With reduction of their weight their diabetes improves and less insulin is needed. On the contrary, lean diabetics must adhere to the caloric value represented by proteins 75 grams, fats 90, and carbohydrates 150, and need insulin for support.

On the basis of these principles and of a table giving the composition of foods according to definite " helpings," diet can be prescribed and the tolerance tested. The sugar content of the 24-hour urine is determined. If the patient has ingested, say, 150 grams of carbohydrate and his urine shows 50 grams in the 24 hours, his tolerance is 100, and so on.

In the diabetic dietotherapy " special diet days " can be introduced. According to individual features these can be green vegetable days, milk days, or even cereal days, according to the von Noorden technique. Starvation days are now indicated only exceptionally. One or two " special diet days " per week often confer great benefit. They act by metasyncrisis, to use the term of the

Greek physicians of the Asclepiadean school, or umstimmung, vegetative alteration or shock in more modern language.

Insulin is given when the diabetic does not improve on simple dietetic adjustment. It is my impression that insulin is much abused and that many diabetics could very well dispense with it. The technique of insulin administration is so special that it can be given here only in general outline.

Insulin treatment must be instituted in a nursing home. The choice lies between protamine zinc insulin or any other insulin of slow absorption, and ordinary insulin. Protamine zinc insulin is the more biological agent. It is absorbed more slowly and thus is a truer echo of normal insulin secretion from the pancreas. Ordinary insulin is absorbed rapidly and thus has more immediate effects. Hypoglycæmic attacks occur more easily from ordinary insulin than from protamine zinc insulin but may be a very much delayed effect of the slower agent. As a general rule protamine zinc insulin is for use in diabetes of medium severity, a combination of the two being indicated in more severe cases. Dosage, which is fixed according to the condition of the patient, is always low at first. Protamine zinc insulin is injected before breakfast, ordinary insulin before breakfast and dinner, and in some severe cases in an additional small dose before retiring. The morning dose decreases the tendency of the blood sugar to rise in the early morning hours; the bed-time dose enables the diabetic to wake up with a sugar-free urine.

Dosage is increased or lowered according to the findings on urine examination, or more precisely of blood examination, for sugar. In severe cases the urine is tested every two hours, in less severe cases every 24 hours. The rough qualitative Benedict test is adequate, a red colour corresponding to + + +, yellow to + +, and green to +.

The patient must be watched for symptoms of hypoglycæmia. These consist in headache, general weakness, listlessness, shakiness of hands and knees, palpitations of the heart, hunger, dimness of vision or double vision, sweating, feeling of heat, flushing, full pulse, and if the condition progresses there occur staggering like that of a drunken man, difficulty in moving limbs, muscular twitching, oppressed breathing, and nervousness. Care should be taken to differentiate these symptoms from those of diabetic coma, a differentiation given above. Treatment of hypoglycæmic accidents consists in administration of sugar and in severe cases of injections of adrenalin or pituitrin.

Insulin is not the only medication for pancreatic diabetes, although at present it is the most important. Albert Robin used colloidal metals in injection, and through their general metabolic shock action these improved many patients. Similar effects are given by various protein shock preparations, hence the good results of vaccines in this disease. Alkalis, biological nervous sedatives and phosphoric acid are good adjuvants.

Spa treatment is of the greatest importance and except in very severe cases should always be prescribed. Choice of spa is based on the special features of various mineral waters. According to individual features, Vichy, Vittel.

La Bourboule, Harrogate or Bath is selected. High altitude health resorts, particularly those of the Engadine, often prove far more beneficial than spas.

Therapeutics of Diabetic Acidosis. 1. The three immediate measures are warmth, circulatory stimulation, and an enema or aperient. Warmth in bed with hot-water bottles is necessary because the temperature falls below normal. Digitalis is indicated only in myocarditis with auricular fibrillation. An enema or aperient is necessary for elmination of poisons. 30 to 40 grams (about 1 ounce) of sodium sulphate or the B.P. magnesium sulphate enema should be given.

2. Glucose-insulin, the basic procedure, is administered at once. 50 to 100 grams of glucose are necessary, and can be given by mouth in the form of lumps of sugar, orange juice, milk, or by enema (Murphy's drip method) or even intravenously. If too little glucose is given the patient may pass from acidosis to hypoglycæmic coma. Insulin must be injected in heroic doses, 50 units subcutaneously in pre-comatose states, 100 units in more severe cases, and even 100 units intravenously, but only after precise determination of the blood sugar. Whenever possible the urine must be examined (catheterisation) and the blood.

3. Abundant administration of fluids completes the immediate measures. It is necessary to combat the dehydration so pronounced in diabetic coma and to drive away poisons. Fluids are given by mouth and by rectum (with the glucose solution) and intravenously in the form of normal or hypertonic sodium chloride solution.

4. The subsequent treatment bears principally on glucose and insulin. The urine should be examined one hour after the above emergency measures have been taken. There follows a rough table of the glucose and insulin rendered necessary by various urine findings.

Acetone + + +	Glucose + + +	50 units of insulin. 50 grams of sugar.
Acetone +	Glucose + + +	Adequate insulin (say 30 units) Less sugar.
Acetone + + +	Glucose +	Less insulin. More sugar.

5. When acetone has disappeared from the urine and symptoms have improved a milk diet or the fruit-vegetable diet can be given and carbohydrate progressively increased, always with the aid of insulin.

CHAPTER L

PANCREATIC HYPOGLYCÆMIA

Hypoglycæmia is the converse of diabetes. Its introduction into nosography is due to Seale Harris in 1923. Like diabetes, hypoglycæmia results from a rupture of balance between the neuro-hormonal systems which regulate carbo-

hydrate metabolism. Either the insulin system is in hyperfunction or the contra-insulin systems diabetogenin, adrenocortin and thyroxin are in hypofunction. To these, therapeutic hypoglycæmia due to insulin injections is added.

Pancreatic hyperinsulinic hypoglycæmia was first studied in 1927, when Wilder and his associates reported the first case of hypoglycæmia connected with a hypersecreting pancreatic tumour. The hyperinsulinism responsible for this form of hypoglycæmia may originate either in the glandular or in the cerebral centre of the vago-insulin system.

Hypoglycæmia sets up numerous disturbances, principally nervous, probably because insufficient fuel-sugar reaches the nervous system, which is very sensitive to this deficiency. Lesions of the cerebral cortical cells, purely parenchymatous and resembling toxic encephalopathy, have been found in cases of fatal hypoglycæmia. The fact that hypoglycæmia occurs in attacks has not been satisfactorily explained. In the case of hypersecreting pancreatic adenomas it is possible that physical exertion or violent nervous stimulation causes intense insulin hypersecretion. It is also possible that insulin hypersecretion is permanent but temporarily arrested or diluted by ingestion of food.

Fat metabolism also is disturbed in some cases, fat storage being accentuated and resulting in obesity. This is probably due to over-nutrition, to which these patients resort to avert their attacks. It is not known whether insulin itself has an anabolic action on fat metabolism or whether a disturbance of the fat-metabolic factor of the pancreas (lipocaic) intervenes.

Primary Pancreatic Hypoglycæmia.

Pancreatic hyperinsulinic hypoglycæmia is determined by a hypersecreting tumour of the pancreas, usually an adenoma of the islets of Langerhans but more rarely a carcinoma of the same formations. Such tumours can originate in ectopic pancreatic tissue—an important fact from the surgical point of view. In an exceptional case seen by Seale Harris a pancreatic hyperinsulinic hypoglycæmia with epileptic manifestations was caused by trauma involving the pancreas.

Paroxysmal Attacks. The disease is characterised essentially by paroxysmal attacks. Although a typical major attack, an epileptiform or unconsciousness attack may mark the onset of the disease, in the beginning they seem usually mild and taken for attacks of weakness or nervousness. There are spells of weakness with hunger, sweating, nervousness and thick speech. Such mild atypical spells may occur for years before a more characteristic attack gives the clue for a precise diagnosis. In a case at the Mayo Clinic such spells occurred for 38 years before consciousness was lost in an attack. In some cases, however, the initial crisis is a major one and thus more characteristic, an attack of " epilepsy " or unconsciousness

These paroxysmal attacks show the five cardinal hypoglycæmic modalities. These are (*a*) occurrence late after meals, when the buffer action of food has waned; (*b*) aggravation by physical and mental exertion, because such pro-

cesses use up sugar; (*c*) relief from food, particularly carbohydrates; (*d*) association with hunger; (*e*) low level of blood sugar.

In these primary pancreatic cases the attacks usually occur in the morning before breakfast, and more rarely late after meals. This is the reverse of events in cerebro-pancreatic and other neurogenic hypoglycæmias.

Attacks of weakness, nervousness, giddiness and petit mal. In the case of pseudo-hysterical attacks the patient suddenly, in the course of perfect health, becomes weak and dizzy. He feels intense hunger and often nausea. His vision becomes blurred and his speech thick. He often yawns, his hands and feet go to sleep, he feels drowsy. Sometimes a sort of petit mal occurs. During conversation or a game of bridge, for instance, the patient stops, seems for a few minutes foreign to his environment, cannot understand or follow conversation. The hypoglycæmic modalities (occurrence late after meals, sensation of hunger, relief from food and association with hunger) are distinct. These attacks may last from a few minutes to half an hour. They cease spontaneously or after taking food, or they may be followed by a major attack such as convulsions. They may constitute the whole clinical picture or alternate with major attacks. They occur irregularly and their number varies. These special pseudo-hysterical manifestations of hyperinsulinism should be considered in the differential diagnosis of " nervousness." This is all the more important in that the attack may be much less distinct than the one described. It is often a simple spell of feeling dizzy and " sinking," with yawning. Some women are so weak before breakfast that they can do nothing. After meals they improve for an hour or two but relapse into fatigue and retire to bed.

Epileptiform convulsive attacks may be ushered in by prodromic symptoms such as pallor, diplopia, irritability, disorientation, numbness of the legs. These become evident suddenly while the patient is busy at his usual occupation. Soon he falls or lies down. He grimaces, tosses about on the bed, clutches the hands of those around him. His eyes are open but he does not seem to recognise his environment. He looks and behaves as though in a dream. He is pale and perspires profusely. Convulsions set in. They are usually generalised but may localise on one side of the body. The body is tossed about with violently kicking legs and flailing arms. Nystagmoid movements are observed. There is much moaning. Excessive salivation brings froth from the mouth. There is no control over bladder or bowel. Blood pressure rises a little but pulse and respiration rates are unchanged.

The convulsive attack lasts minutes or even half an hour or more and is followed by a period of relaxation. Hemiparesis may follow. The speech is noticeably slurred. After a few hours of normal sleep the patient feels well but tired and apathetic, and the speech remains slurred. Death can occur during the attack.

A bilateral or unilateral Babinski extensor reflex can be observed during such attacks. Tendon reflexes during and after the attack are strong. Abdominal reflexes are not distinctly modified.

Sevringhaus, Schmidt and Bast have published an interesting observation

of a patient whose status epilepticus was relieved by removal of a carcinoma of the tail of the pancreas.

Attacks of abnormal behaviour are illustrated by two observations giving the essential characteristics of this form of attack.

A case of A. D. Carr and others refers to a cadet in a military school. On one occasion he heard the morning bugle but nothing more until he found himself being examined. In the meantime he had dressed clumsily, had reached the mess hall and began to eat so awkwardly that it was recognised that he was ill. He was taken to the school hospital, where he slept for 36 hours and recovered completely. On another occasion the same patient drove for 45 minutes along busy streets and had no remembrance of doing so.

The other case was seen by Rynearson. It refers to a farmer who, on arriving at the bazaar, found he was too late to assist with the milking. So he filled the pitcher with milk and pumped a pail of drinking water. When he arrived in the house again it was noticed that he had a strange look on his face. He began washing his face in the bucket reserved for drinking and when asked why, appeared to have no idea of what he was doing. The wash-basin was handed to him. Thereupon he poured the cream into it and started washing his face in the cream. He undressed, went to bed, and awoke four hours later, remembering nothing of the entire incident except the queer colour of the waste water and his difficulty in getting upstairs.

According to Wilder, crimes and offences have been committed during hypoglycæmia.

Comatose attacks sometimes occur before the patient gets up, and he is found in bed unresponsive but with wide-open eyes. He recovers when sugar or orange juice is forced into his mouth. In other cases such patients feel suddenly weak while pursuing their normal occupations, perspire profusely, and their stupor merges into deep coma. The duration of comatose attacks varies. Power and his associates reported a case in which the coma lasted 30 hours and recovery was brought about by intravenous glucose. Residual symptoms such as weakness of arms or legs and slurring of speech may persist.

Minor visceral attacks, attacks of hunger pain. The hunger pain simulates that of ulcer and occurs late after meals. It is quite frequent, and the diagnostic errors it causes are obvious. Attacks of tachycardia and palpitations also are noted.

The Chronic Condition. During the interval between attacks there is no particular clinical finding. The health of these patients is good, and the nervous system does not show the instability evident in cerebro-pancreatic hyperinsulinic hypoglycæmia. In some cases, however, it is not rare to see, even after many paroxysms, a chronic mental syndrome of instability, of mental deterioration, of coarsened character, vulgarity in speech and deportment, inability to get on harmoniously with others and extreme annoyance at trivialities.

Biochemical findings are more characteristic. Hypoglycæmia is usually found in the morning, indicating a low post-absorptive level. Fasting hypo-

glycæmia is peculiar to the pancreatic forms and less marked in cerebral forms. On glucose tolerance test a typical flat curve is obtained. Two hours after ingestion of glucose the blood sugar falls very low, and values may be lower than the fasting hypoglycæmia of the same patient. Hence a severe hypoglycæmic attack may follow this test. This symptom, however, is more frequent in cerebro-pancreatic hyperinsulinism.

Therapeutics. The hypoglycæmic attack is treated by administration of fair quantities of sugar or any other carbohydrate food, in severe cases by injection of ephedrine and intravenous glucose.

In the chronic condition it is better first to assume that the pancreatic hypoglycæmia is non-neoplastic and to use dietotherapy, the only internistic procedure known for that condition. Two methods can be employed. A high carbohydrate diet gives temporary relief but aggravates the condition by stimulating insulin secretion. A high fat low carbohydrate diet has been advocated on the ground that carbohydrate absorption is retarded and diminished and insulin secretion not stimulated, but this method is not always successful.

When dietotherapy fails and the condition becomes serious, resort should be made to surgery. This is curative in neoplastic pancreatic hypoglycæmia but only palliative in non-neoplastic or cerebro-pituitary states. In neoplastic conditions the tumour is removed, in non-neoplastic cases a certain amount of pancreas is excised so as to rid the patient of as much hypersecreting pancreatic tissue as possible.

Cerebro-Pancreatic Hyperinsulinic Hypoglycæmia.

In this form the whole vago-insulin system is in hyperfunction beginning at the diencephalic centre. The usual interplay of constitutional lability of the vago-insulin system and of environmental factors, dietetic and mainly psychological, upsetting this system is responsible. A similar mechanism can be accepted for other " functional " hypoglycæmias due to hypofunction of the contra-insulin systems, mainly the sympathetico-hepatic.

This form is characterised by similar but milder and less typical paroxysmal attacks. Visceral forms are interesting. I have seen individuals with attacks of angina pectoris occurring after meals who obtained immediate relief from glucose and permanent relief by means of low carbohydrate and high protein diets. Certain attacks of migraine also improve on glucose and thus probably belong to this class. Sensations of extreme weakness and dizziness two or three hours after meals are frequently of hypoglycæmic nature.

The general characteristics of these attacks offer certain peculiarities. They seem related more to the intake than the withdrawal of food. Whereas pancreatic hyperinsulinics do not tolerate fasting and when deprived of a meal enter into paroxysms, cerebro-pancreatic hyperinsulinics tolerate fasting well and do not have attacks simply from missing their food. For this reason these subjects have no disturbance at night and their attacks do not occur in the morning before breakfast. On the contrary, the food stimulus causes an

abnormal hypersecretion of insulin and attacks occur three to four hours after meals.

Another essential feature is elicited by investigation of the personality of the patients. They lack the usual interparoxysmal perfect health of pancreatic hyperinsulinics, but show evidence of autonomic instability, intense nervosity, and complain of chronic fatigue.

Biochemical exploration less frequently shows intense fasting hypoglycæmia but glucose administration gives either a flat hypoglycæmic curve or, after allowing a very slight rise in blood sugar, shows a fall much more intense than in pancreatic cases and resulting more frequently in a hypoglycæmic attack.

Treatment principally consists of psychotherapy and dietotherapy with the adjunction of medicines like atropine, phenolbarbital and strychnine.

SYMPTOMATIC AND OTHER FUNCTIONAL HYPOGLYCÆMIAS

Symptomatic Hypoglycaemias. Hypoglycæmia is encountered in Simmonds' disease more or less as a characteristic, and is due to diabetogenin insufficiency. Clinically it shows certain similarities with the features of neoplastic pancreatic hypoglycæmias, except that it occurs in the course of a more or less characteristic Simmonds' disease. The milder attacks consist in giddiness, headache, strange transient psychical disorders during which these patients are distrustful, querulous and may have delusions. More severe attacks consist in delirium and restlessness, a sort of acute psychotic condition, violent psychotic anxiety and motor restlessness or even convulsions. It is to be remarked that low levels of blood sugar occur in Simmonds' disease and in chromophobe adenomas of the pituitary without any symptoms. It seems that an extensive destruction of the antepituitary is necessary before any disturbance of the regulation of blood sugar can be detected. It is obvious that insulin administration accentuates or provokes such symptoms, hence the insulin hypersensitivity encountered in Simmonds' disease.

Hypoglycæmia is seen in Addison's disease. Its clinical features are also those of pancreatic hypoglycæmia except that they occur in the course of a more or less characteristic Addison's disease. It is due to disturbance of the adreno-hormonal regulation of metabolism allowing insulin to act unchecked. Hence an insulin hypersensitivity similar to that of Simmonds' disease.

Hepatic hypoglycæmia is encountered in extensive hepatic destruction. Glycogen and glucogenolytic enzymes are absent, and thus blood sugar is deficient. Judd and others have reported two cases of spontaneous hypoglycæmia associated with fatty metamorphosis of the liver. A fatal hypoglycæmia due to neoarsphenamine has been attributed to hepatic destruction by Cross and Blackford. The question has been reviewed by Colles and Jackson. The existence of sympathetico-hepatic hypoglycæmia, *i.e.*, hypoglycæmia due to inhibition of the sympathetico-hepatic glycogenolytic system, is not known.

Myxœdema hypoglycæmia is rare but must be considered as a possible diagnosis.

Functional Non-pancreatic Hypoglcaemias. It is possible that hypoglycæmias similar to cerebro-pancreatic hypoglycæmia occur on account of hypofunction of one of the contra-insulin hormonal systems, and thus functional cerebro-pituitary, cerebro-pituitary adrenal and neuro-hepatic hypoglycæmias can be accepted. Diagnostic and therapeutic considerations do not differ from those of cerebro-pancreatic hyperinsulinism.

CHAPTER LI

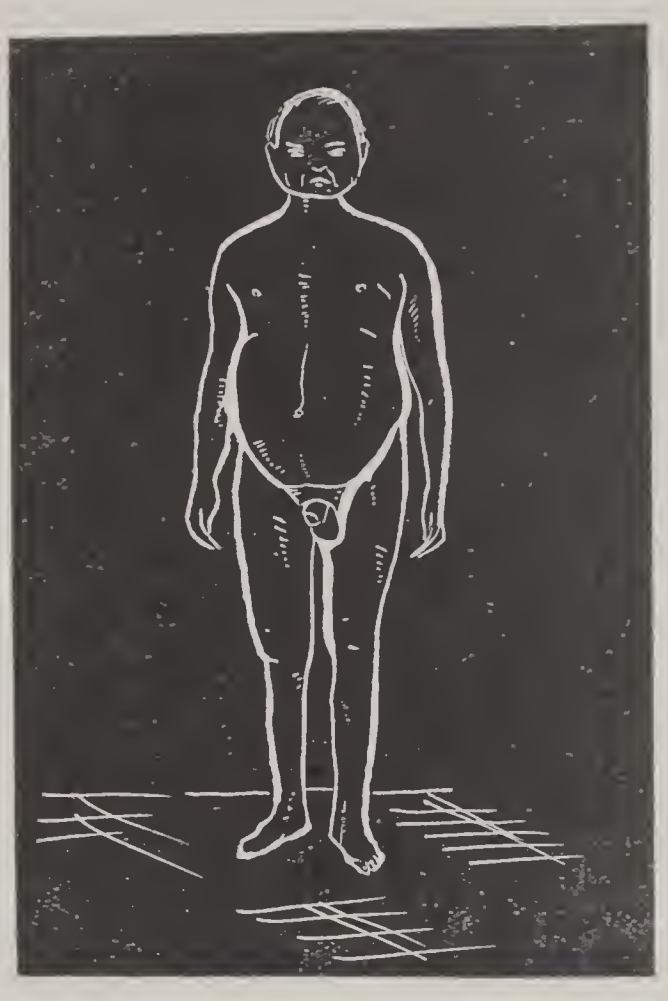
HEPATO-PANCREATIC OR NUTRITIONAL OBESITY

Physiopathology and Etiology. Nutritional obesity is bound up with excessive food intake, lack of movement and exercise, and insufficiency of the hepatic and pancreatic fat-catabolic functions. A genetic element of adipose cell lipophilia may co-exist. This form is often described as exogenous obesity, but the term is not adequate because much depends on the capacity of the individual to metabolise the excess of food. Many individuals eat heavily, perform no physical activity but do not become fat, while others, who eat less and are slightly more active, become obese.

Nutritional obesity occurs in both sexes, and particularly in persons whose work and mode of life are sedentary and permit an excess of food. It is encountered in pampered children who are showered with sweets, and in adults who indulge in the pleasures of the table or, after an active life, take up office work. It occurs in convalescents who build up their strength too quickly. Hereditary and familial elements are noted even in this form of obesity. Heredity may have conferred bad alimentary habits but also may have transmitted defects in the genetic nervous and hormonal regulators of fat metabolism, for there is always an endogenous element in the " exogenous " obesities.

In such individuals a real perversion of appetite, a hyperorexia, a boulimia, is often encountered and may reach a high degree. Grafe cites the case of a patient consuming 12 pounds of meat daily in addition to the usual foods. This craving for food may be of psychogenic origin. For some people life is very difficult. They struggle with a problem, sexual, social or financial, for which they can discover no solution, but they find that they obtain temporary solace in eating and in alcohol. In children over-protection leads to bad alimentary habits. An exaggerated anxiety and misinterpretation of the medical situation result in parental conduct depriving the children of most of their normal outlets and making them self-centred and prone to regard themselves as objects of pity and special consideration. Under such circumstances the satisfaction derived from eating is the only pleasure still permitted to these children. The young patient suffering from self-pity and egoism accepts food even if he has no desire for it. As time passes conditioned reflexes become

firmly developed and the feeling of satiety does not occur easily. Investigation of obese patients on the basis of these data reveals that as children they were over-protected, that, for instance, at an advanced age they were incapable of dressing themselves and were bathed by their mother. Excessive eating is an expression of a mood, a behaviouristic response to the patient's environment.



NUTRITIONAL OBESITY

The basic metabolic disturbance determined by dysfunction of the nutritive, hepatic, pancreatic and, up to a point, the genetic regulators of metabolism is an intensification of fat storage in the depots and deficient lipolysis from the adipose cells of the depots. To this lipophilia is added hydrophilia of the fat depots, which in nutritional obesities is explained by the fact that fatty tissue absorbs water like a sponge independently of any circulatory disturbance and with no evidence of œdema. The fluid content of human fat shows enormous variations ranging from 5–71 per cent.

Basal metabolism may be normal or low. When it is diminished this is due not to a concomitant thyroid deficiency but to the difficulty with which fat tissue releases its contents for the production of energy in obesity. Hence an economic restriction of metabolism. In some cases diminution of the specific dynamic action of food is noted, indicating a concomitant deficiency of the antepituitary metabolic hormone. The normal individual is capable of coping

with emergencies inherent in environmental-dietetic conditions and readily adapts himself to over-eating or under-eating by a change in the intensity of oxidation, which decreases in starvation and increases in over-nutrition. The increase in oxidation after intake of food is particularly conspicuous upon ingestion of proteins, and may rise to 46 per cent. This mechanism is defective in some obesities belonging to this class.

The other metabolisms are not much disturbed. Nitrogen is increased in the urine, but this is due to over-nutrition. Carbohydrate metabolism is disturbed in the direction of carbohydrate intolerance, diabetoid and diabetes, this indicating a concomitant involvement of the vago-insulin system.

Clinic. Adiposis varies in degree from 10–20 per cent. overweight to higher figures which, however, do not reach those of pituitary obesity. Severe cases are termed the Falstaff type. It is generalised, although it often spares the extremities. It involves particularly the abdomen but not the hips. The co-existence of a neuro-vegetative-lipophilic or a genetic lipophilic element, however, may direct the adiposis to predominate in certain regions.

Predominance of the hepatic element is indicated in some cases by special morphological features. The skin is sallow, the eyelids in particular are pigmented (the hepatic spectacles of the French clinicians). Red capillary nævi (taches rubis) soon develop on the skin. The capillaries of the face are dilated, constituting a sort of cutaneous vascular spiderweb. Small violet varicosities follow the insertions of the diaphragm and form something like a belt. The sclerotics are yellow.

Psychologically these individuals are of phlegmatic temperament, lacking the intense emotionality of pituitary obesity. The phlegmatic temperament is a personality trait and contributes to adiposis because emotions increase metabolism. When the hepatic element is important, irritability is noted. On the whole, however, in spite of their phlegmatic temperament, sufferers from nutritional obesity are very sociable and great " bons vivants."

In their reactions these patients are lazy but not asthenic. They move with difficulty because of their fat and temperamental laziness. They often perspire easily and feel the heat. They show great lack of resistance to pneumonia.

Digestive disturbances are frequent and due to over-nutrition. Constipation occurs and is due mainly to fat infiltration of the abdominal and colon muscles, already hypotrophied through sedentary habits, and to fat infiltration of the wall of the gut. The frequent but mild circulatory disturbances are due to fatty infiltration of the heart (the beer heart of German authors), not to any defect in hormonal regulation. Blood pressure is normal. Nervous symptoms are absent.

The biochemical findings are not very characteristic. Basal metabolism is normal except for the diminution due to excess of fat tissue, which is of low metabolic activity. In purely nutritional obesity there is no important retention of water or salt. The urine shows excessive nitrogen due to over-nutrition.

The course of the disease depends on continuation or cessation of the faulty

alimentary and hygienic habits. When alimentation continues to be excessive the disease persists. Such patients may succumb to pneumonia or any other infectious disease. Diabetes may supervene, and other disturbances may result from the excessive nutrition.

NUTRITIONAL OBESITY

Shakespeare has given us in Falstaff the most precise delineation of the accentuated form of this nutritional (and bibational) obesity, depicting the special distribution of fat, the large abdomen ("How long is it ago, Jack, since thou sawest thine own knee?"), and the phlegmatic temperament combined with sociability and laziness.

Therapeutics. Only the general principles can be laid down in a work of this sort. Details of technique are given in special works.

The treatment of nutritional obesity consists in (*a*) regulation of the appetite and dietetic habits; (*b*) a special dietotherapy based principally on a low caloric content; (*c*) kinesitherapy and other physical methods; (*d*) medicines stimulating hepatic, pancreatic and digestive functions, particularly intestinal elimination, and agents accelerating metabolism.

(*a*) Regulation of the appetite and dietetic habits of the obese patient (eating between meals) is the basis of the first therapeutic requirement. Appetite restriction is often a matter for psychotherapy. It can be helped by medicines such as belladonna tincture and benzedrine, although the latter should

be used with great care especially as its effects are very problematic. It can be helped also by allowing the patient to take such " foods " as Bovril, which bring a feeling of satiety but have no caloric value. The 3–5 per cent. vegetables have the same helpful action.

(*b*) The second and probably most important therapeutic requirement, administration of a special diet, also must be preceded by careful investigation of the dietetic habits. The principle is to give foods of low caloric value. Proteins should be given in adequate quantity. Fats and carbohydrates must be restricted. Salt also must be restricted, although not to the degree necessary in diencephalo-pituitary obesity. Water is limited to the same extent. Vitamins should be given in the necessary and balanced amounts. An important principle, in my opinion, is to avoid the indiscriminate combination of foods. The meat-fish, meat-egg and egg-fish combinations should be particularly avoided. Thus at any one meal meat or fish or eggs can be taken but never two of these foods.

For details of the application of this diet the reader is referred to special treatises on dietotherapy. Some guidance among the complicated expositions of diets for obesity, however, can be indicated.

In mild cases the " dietetic chart method " can be used. A comprehensive chart of foods, such as I devised for my own practice and the St. John Clinic, is given to each patient and the foods rich in calories are struck off.

In more severe cases the " skeleton 1,000 calory diet with progressive addition of 100 calory portions " is used. A special diet providing 1,000–1,200 calories is prescribed and according to clinical indications it is increased by the addition of 100 calory portions.

In both mild and severe cases the " dietetic days method " can be employed. This consists in giving patients on the " dietetic chart " or even the " skeleton diet " method a specially restricted diet on, say, two days each week. This may be a milk diet (4–5 pints daily) like the Carrel diet, an exclusive fruit-vegetable diet, or the banana-milk diet. I have no experience of the severely restricted diets advised by Evans and Strong. Starvation days are not always effective in this form of obesity and should be used only in exceptional cases.

(*c*) The third therapeutic requirement, application of physical methods, consists, as I have indicated in a recent paper on the subject, in directing the patient to walk, to indulge in certain sports, and in general to perform certain pleasurable physical activities. I insist on the pleasurable element, because I do not believe in the exclusive myotherapy used by Francis Heckel in the treatment of obesity. Brisk walks in the country and mountain-climbing, provided they are not followed by excessive food intake, are really helpful, whereas the abdominal exercises which obese business men or middle-aged women perform daily in their bathroom have no effect at all. The same can be said of the strenuous week-end golf with which city men try to counteract their sedentarity. Treatment in nutritional obesity is directed to the nervous system, thus to the neuro-muscular apparatus, not to the muscular fibres alone.

Strong muscular massage may help the masseur to lose weight but not the

patient. Effleurage, however, is a good general metabolic stimulant. Ultraviolet irradiation and foam baths also are excellent general metabolic stimulants. The Bergonié method of electrical " exercise " has very limited indications. It is good in certain cases of extreme obesity in which the patients cannot move easily. It acts more especially by the nervous reflexes it provokes and is thus a shock treatment or reflexotherapy. It does not act by " exercising " the patient, for the only good form of exercise in obesity is active exercise.

Crenotherapy is a valuable adjunct to treatment of nutritional obesity. The diet, mental calm and physical methods which compose spa treatments form the basis of the good results. Further, spas are valuable centres of education for obese individuals. Certain mineral waters also act, however, on hepatic and intestinal functions and thus contribute to the cure of obesity. High altitude climates are effective through their stimulating action on metabolism, and also probably through their action on the vegetative nervous system—provided diet is kept low in these resorts.

(*d*) For the fourth therapeutic requirement hepatic stimulants of the Agocholine type are valuable, as also are alkalies in the form of a mixture of sodium sulphate 3·0, sodium phosphate 1·0, sodium bicarbonate 1·0 taken in a tumblerful of cold water in the early morning. Laxatives should be used in constipation. Thyroid, not in large doses ($\frac{1}{2}$–1 grain per diem) is the best metabolic stimulant and is usually well tolerated.

CONFINIA ENDOCRINOLOGICA

CHAPTER LII

THE CONSTITUTIONAL AND ENDOCRINE METABOLIC FACTOR IN DISEASE

Having studied the natural history of endocrine diseases we must turn once more to consideration of the whole system of constitutional regulation, for outside its frame endocrine physiology and pathology cannot be understood. Endocrine nosography helps to an exact understanding of the endocrine factor in disease in general, and more particularly to an understanding of the constitutional factors. Through it study of the natural history of diseases is enlarged and new vistas are opened.

A few years ago, when endocrinology was showing its great possibilities, Professor Leriche of Paris wrote that it was time to review nosology, *i.e.*, the science of diseases, in the light of endocrinological discoveries. With the enlargement of the endocrinological point of view into the constitutional point of view it seems justifiable to ask for a revision of nosology in the light of the constitutional outlook.

We have described a system of constitutional regulation which, when predominantly involved pathologically, gives rise to the so-called constitutional diseases. According to the component of this system in which morbid localisation occurs, endocrine diseases, genetic diseases, psychogenic diseases, avitaminoses and others are distinguished.

This separation of constitutional diseases, although effective in practice, is artificial. The constitutional regulatory system is involved in all diseases, because it is the system through which humans adapt themselves to their environment, and disease consists in a defect of this adaptation. However, from the practical point of view there are cases in which the constitutional involvement is less apparent clinically, the terminal effect of this constitutional involvement, the organic localisation, being more marked. These are termed organic as opposed to constitutional diseases. The distinction is artificial, however, because all organic disturbances and lesions, and thus all organic diseases, are determined by metabolic or chemical disturbances of the body set up by a primary dysfunction of the system of constitutional regulation. Thus in reality there are no constitutional or organic diseases but a constitutional or organic point of view in disease. It follows that in the so-called organic diseases the primary constitutional disturbance—metabolic, endocrine, neuro-vegetative or psychogenic—must be considered. For this reason our nosographies should be revised.

As far back as 1870, Albert Robin wrote that the organic localisation, which was the principal object of study of his contemporary clinicians of the French anatomoclinical school, did not interest him. He considered that prior to the organic localisation there occurred chemical metabolic disturbances in the body, and his efforts concentrated upon studying these disturbances and acting upon them as the most effective way of fighting the "disease," the organic localisation. Many clinicians have since followed that line of action, the introduction of this constitutional outlook making many changes in the science of disease. These changes bear on all chapters of the natural history of diseases, the etiological, the physiopathological, the symptomatological and the therapeutic.

It should not be thought that all the principles discussed here are essentially new. Most of them are resuscitations of old ideas, particularly of the Hippocratic ideas. Most of them have been accepted by the great clinicians of the ages. It is rather in relation to our immediate predecessors that most of these principles are new.

New trends in the etiology of disease introduced by the constitutional outlook. In the nosographical textbooks, the "Practices of Medicine" of the Anglo-Saxon world, the "Special Pathologies" of the European continent, etiology centres on the environmental factors and, particularly since the discoveries of Pasteur, on bacteriological infective factors. This exclusive role of the external factors, this physiopathology considering the organism as an inert substance whose reaction depended on the intensity of the external factors, could not endure. In England and France the Hippocratic doctrine of diathesis

was reintroduced. Bacteriologists such as Hueffer showed that in infections the soil was as important as the agent. A uniform causalism was in general replaced by the "conditionalistic" conception according to which disease was due not to one factor alone but to a series of etiological conditions, amongst which factors of constitutional predisposition were gaining in importance.

It has been demonstrated that individuals showing certain constitutional features, individuals of a particular constitutional type or biotype, have a predisposition, a diathesis, to certain diseases. In other words, given certain environmental factors these individuals will react by a particular "disease." Thus persons with constitutional features based on hypogonadism are found amongst patients with peptic ulcer. A new line of research has thus opened in the etiological chapter of diseases, aiming at discovering the constitutional features—mode of function of psyche, endocrines, neuro-vegetative system, genetic hereditary influences—which make for a diathesis for the particular disease. In the next chapter we shall develop the line of research aiming at isolation of special constitutional types or biotypes. The etiological chapter of the natural history of disease will develop by discovering which biotypes subjected to certain environmental factors (psychological, infectious, toxic, traumatic, dietetic) show the particular disease described.

New trends in the physiopathology of diseases through introduction of the constitutional outlook. According to the general physiopathological principles accepted to-day, there occurs in disease first a disturbance of the constitutional regulatory system, particularly of psyche, neuro-vegetative system and endocrine system. A series of metabolic disturbances arises with the ultimate result of organic localisation. Further, the organic localisation itself reacts on the system of constitutional regulation by a vicious circle.

In old textbooks the physiopathology of disease was centred on the organic lesion. This was the only event described, and the chapter of physiopathology was called pathology, meaning morbid anatomy. Those were the days of anatomical thinking. Later physiological thinking was introduced. The chapter on pathology-morbid anatomy became a chapter on physiopathology. Consideration was given not only to the anatomical lesion but also to the functional disturbance of the particular organ, the lesion being regarded as the terminal effect of the functional disturbance. To anatomical pathology functional pathology succeeded. To-day we go further. The chapter on physiopathology considers first the disturbance of the constitutional regulators and the metabolic changes resulting from that disturbance which determine the functional disturbance and later, in some cases, the lesion of the particular organ. Physiological thinking in medicine has been superseded by constitutional thinking, and functional pathology has been enlarged into constitutional pathology.

It is of course possible that one and the same organic dysfunction or lesion results from various constitutional-metabolic disturbances. Thus, as I have pointed out in a paper sent to the International Congress of Rheumatism at Moscow in 1934, the lesion of osteoarthritis may be the result in some cases

of a thyroid disturbance, in others of a gonadal. It may be the result of disturbances of sulphur metabolism in some cases, whereas in others sulphur metabolism is normal. It is the role of the student of the natural history of disease to determine whether any one of these constitutional disturbances preponderates, or alternatively the respective roles of the various constitutional regulators involved.

In Bright's disease, *i.e.,* in chronic nephropathy, important constitutional metabolic disturbances are seen. These were regarded as always secondary to the renal lesion, and in fact most of them are. But, as I pointed out in a monograph published in 1910, there are some that must be considered as preceding and determining, in part at least, the renal localisation. Since that date such metabolic disturbances preceding and determining renal localisation have been demonstrated. The disturbance of a neuro-endocrine constitutional regulator, the parathormone system, and the resultant changes in calcium and other metabolisms is at the origin of a particular form of nephritis, hyperparathyroid nephritis. Disturbance of a gene regulating lipoid intracellular metabolism causes another form of nephropathy, lipoid nephrosis. And it is probable that this nephrotic localisation, at all events in some cases, depends on the disturbance of an endocrine regulator also, the thyroid.

The primary constitutional phase exists in all diseases. There are diseases in which it is very important for the understanding of the whole physiopathology. There are others, e.g. infectious diseases, in which it plays a less important role.

Facts are accumulating daily. These ideas are penetrating medical public opinion more and more. We hear of endarteritis obliterans as a " disease of metabolism " (Cawadias), of atherosclerosis as a " disease of metabolism," of rheumatism as an " endocrine disease " (Selye). All this indicates that organic localisation is preceded by constitutional (psychogenic, neuro-vegetative, endocrine, genetic) disturbances, of which the knowledge clarifies much of the mechanism of these diseases.

However, the fact that an endocrine or any other constitutional factor is encountered in any disease does not justify considering this condition to be an endocrine or a constitutional disease. Nosographical divisions must be maintained on the basis of preponderance. Chronic rheumatism, alopecia areata, acne, eczema, myasthenia gravis are not endocrine diseases but diseases in which an endocrine factor often exists. Endocrine diseases are only those in which the endocrine factor is distinctly preponderant, and similarly constitutional diseases are those in which a constitutional disturbance predominates absolutely. Precision in clinical work is not achieved by undue enlargement of the frame of endocrinology. In our individual investigations elasticity is necessary, but this is possible only if precision is maintained in nosographical frames.

New trends in the symptomatology of diseases through introduction of the constitutional outlook. Symptomatology becomes more complete by the adjunction of symptoms referring to the constitutional phase of disease.

Sir James Mackenzie insisted on the necessity of detecting the earliest

manifestations of disease, and devoted much of his great clinical talent to such researches. The earliest clinical symptoms are the manifestations of the primary constitutional phase. With great clinical intuition he considered these earliest symptoms as manifesting neuro-vegetative disturbances. We can go farther. We want to find the symptoms indicating the early disturbance of the entire system of constitutional regulation, the disturbance preceding organic localisation. Thus analytically we must consider manifestations of psyche disturbance, of neuro-vegetative disturbance, of neuro-endocrine disturbance, with their resulting metabolic changes. These are the first pages of the clinical history of the disease, and are waiting to be written. They are pages of the greatest importance for prognosis and treatment.

The necessity of establishing the clinical manifestations of this primary constitutional phase, the earliest phase of disease, has re-orientated interest in the guidance of James Mackenzie to study of symptoms. Gone are the days when a "specialist" thought himself happy because he was deaf and thus could proceed with the physical examination without bothering about the complaints of the patient. More than ever to-day we recognise that the history which the patient tells us is of overwhelming importance, and more than ever we try to assess the symptoms of which he complains. The morbid process in its beginnings is manifested through the delicate reactions of the psyche and the vegetative nervous system. These manifestations are purely symptomatological, because when physical signs occur disease has passed from the constitutional to the organic phase. As many great clinicians, particularly those of the Oppolzer, Neusser and Ortner school have shown, well studied symptoms are of the greatest help in diagnosis. Unfortunately we lack a systematic study of symptoms, for we have been over-preoccupied with the feverish search after signs, particularly laboratory signs, and obnubilated by the false precision of "signs." It demands greater skill to assess the history and symptoms than to note signs. The unwary cannot distinguish shades in painful reactions, in behaviour disturbances, or the significance of an early peculiar family environment. Constitutional medicine has given a strong impetus to the science of symptoms, a science possessed by our ancestors, who without our modern semiological technique could make brilliant diagnoses and treat their patients probably as well as we do to-day. To be a clinician to-day does not mean ability to interpret urinary tests, electrocardiograms and radiographs. This is necessary, but the clinician is made above all by his capacity to elicit symptoms through a special art of interrogation and investigation and to interpret them as manifesting the total reaction of the individual to morbid factors. Professor John Ryle has developed this principle.

New trends in therapeutics through introduction of the constitutional outlook. Consideration of the primary constitutional phase, recognition of the importance of the constitutional disturbance in the genesis of the organic localisation and knowledge of the role of the system of constitutional regulation in the fight against disease have not only enriched but in fact completely refashioned the therapeutic chapter of the natural history of disease.

In days when physiopathology centred on the organic lesion therapeutics oscillated between medical nihilism and surgical radicalism. In fact, the lesion could not be influenced by medical methods and only surgical procedures remained. When, later, physiopathology became centred in the functional disturbance of the organ, a certain amount of functional therapy was applied, but as consideration of an organ isolated from the whole is artificial, methods directed solely to it were not notably effective—witness the acids and alkalis with which " gastric " patients were treated. With the introduction of the constitutional outlook therapeutics gained in power. We know that we can arrest disease at onset if the constitutional regulatory system is helped to restore its balance by medical influence on its psychological, neuro-vegetative, endocrine and nutritive disturbances. We know that even when the organic localisation has been established treatment of the basic constitutional disturbance may restore health. Constitutional outlook, constitutional therapy, have opened new vistas to the patient.

We cannot influence an organic lesion. We can correct with difficulty an organic dysfunction by acting solely on the particular organ; but we can act on the system of constitutional regulation. We can correct psychogenic disturbances through psychotherapy applied with skill and science, not the haphazard psychotherapy of the so-called " commonsense." We can correct endocrine dysfunction thanks to a greatly developed hormonotherapy. We can correct neuro-vegetative dysfunction by various medicines, including the homœopathic medicines which in my opinion rank among the best restoratives of neuro-vegetative imbalance. We can correct nutrition through dietotherapy. We can influence the neuro-vegetative system, the general metabolism and the " competence " of tissue cells by physical medicine, with good constitutional therapeutic effects which I have been watching for years at the St. John Clinic and Institute of Physical Medicine. Constitutional medicine including metabolism and endocrinology has developed with a view to therapeutic possibilities, and these have been amply realised.

CHAPTER LIII

BIOTYPOLOGY AND THE BIOTYPES

Biotypology, the isolation and study of types of constitution, stands in the same relation to healthy humans as nosology to diseased humans. Just as the features common to diseased humans enable us to isolate " types " of disease or diseases, common constitutional features provide a foundation for the isolation of types of constitution or biotypes. Thus biotypology is, like nosology, a method of scientific study. There are no biotype entities, but only individual constitutions, just as there are no " diseases," but only individual patients; but in the same manner as nosology helps us to classify and give precision to our knowledge of diseased individuals, biotypology enables us to

classify and give precision to our knowledge of humans in general.

The reintroduction of the Hippocratic outlook into medicine has stimulated the development of biotypology. In modern medicine it has become important to determine not only what kind of "disease" a patient has but also what kind of individual he is. Biotypology is as necessary for determination of the particular kind of individual as nosology for determination of the particular kind of his "disease."

Definition. Before proceeding to study biotypology, terms must be defined with precision, because inaccurate terminology has hampered many a development of scientific conceptions. As Condillac said: "La science est une langue bien faite," and scientific progress needs essentially the introduction of accurate terms.

Constitution, as already indicated, denotes the whole psychophysical structure of the individual. It is based on the sum total of the chemical processes of the body as regulated by a system of forces delineated in the first chapter of this book, the system of constitutional regulation.

A biotype is a type of constitution. It should not be taken to denote the constitution of a particular individual. The individual constitution is the reality which confronts the physician. Biotype is an abstract creation based on consideration of many individual constitutions showing certain similarities of feature.

Diathesis is the Greek term for predisposition. It is not synonymous with constitution but depends on the particular constitution of the individual. A hypogonadal constitutional type, for instance, may have an ulcer diathesis, *i.e.*, a predisposition to peptic ulcer.

Personality in its wide sense is synonymous with constitution or psychophysical structure of a particular individual, but is taken to mean only the psychological features of that constitution. Temperament, notwithstanding the etymology, also is taken to denote the psychological features of the constitution of a particular individual.

Basis of Classification in Biotypology. It is obvious that the basis of constitution, individuality or personality in its wide sense is the mode of function of the system of constitutional regulation.

The isolation and thus the biotypological classification of types of constitution have encountered the same difficulties as the isolation of types of disease, and similarly a general criterion cannot be accepted at present.

Types of humans, thus types of constitution, have been described on the basis of morphological features, of habitus. This basis has been used for the isolation and classification of human types by Rostan, Da Giovanni, Beneke, Sigaud, and Stockard. F. Kraus also classified constitutional types according to this purely morphological criterion, which he developed by the addition of precise anthropometrical measurements following the technique of the anthropologists.

This method has been adopted also by Viola, T. Brugsh and G. Draper,

and more recently by Sheldon. The morphological criterion permits isolation of types of habitus but not types of complete human constitution. Man is something more than pure form, and a purely morphological classification is clearly as insufficient as a nosographical classification based, for example, on symptoms referring to one organ.

The same argument applies to all endeavours to isolate types of humans on the basis of one feature alone; thus, to Jung's attempt to isolate biotypes on the basis of the psychological features only and to divide humanity into introverts and extraverts, and to the researches of Eppinger and Hess separating human beings into sympatheticotonics and vagotonics on the basis of their neuro-vegetative reactions.

Biotypology made great progress after the last war when Kretchmer described human types according to the combination of morphological and mental features. This work also made evident the remarkable connection between these two groups of features. The research of G. Draper and of Sheldon also proceeded along these lines.

Shortly after Kretchmer's work I proposed in my Athens lectures a biotypological classification of the individual based on the mode of function of his endocrine system, and at the same time, Pende, in Genoa, developed his biotypology on similar lines. I pointed out that as both habitus and mental features are manifestations of the mode of function of the endocrine system, the isolation of human types according to the criterion of endocrine function was more rational. The work of Berman proceeded on these lines.

However, this criterion also is proving insufficient. In the first place, since the days when an endocrinological biotypology was proposed the exclusively endocrinological point of view has yielded to the constitutional point of view. Thus if a basic physiological function is required as a criterion of biotypological classification, the whole function of the system of constitutional regulation must be considered and not only the endocrine function. Now, the mode of function of the system of constitutional regulation can be expressed either by indicating the predominance of any component of that system—the endocrine component, for instance, or by indicating the totality of clinical manifestations. The new method of isolating biotypes and classifying biotypical units combines thus the lines followed by Kretchmer and those indicated by Pende and myself in the early 'twenties. It enlarges Kretchmer's method by the addition of factors other than the morphological and mental (effected by G. Draper's happy conception of panels of personality) and it tempers the exclusively endocrinological views of Pende and myself by its emphasis on predominance and its total consideration of the constitutional regulatory system.

According to this criterion the following biotypes can be described. It is unnecessary to add that this classification is incomplete, and is given only as a directive line for future research. Even as it stands, however, it helps in understanding " the patient who has the disease."

The Harmonious Biotype, the Canon.

This corresponds to a perfect balance of the system of constitutional regula-

tion, the ἰσονομία of Alkmeon (sixth century B.C.). It is not an average emerging from statistics but an ideal.

Morphologically these individuals show the height and weight regarded as normal and perfect symmetry of all parts of the body. These morphological features are embodied in the famous Doryphoros or Canon of Polycletos, a celebrated sculptor of Argos in the fifth century B.C. Polycletos depicted in his Canon all that he considered united in the normal or ideal human form, and wrote a book to illustrate his conceptions. The book has been lost but copies of the statue still exist. On the basis of the Canon of Polycletos the physician Galen wrote a fine chapter on the normal human form. Both Polycletos and Galen insisted, apart from the harmony or proportion, on well-developed muscularity as representing normal man. The muscularity, however, should be developed in harmony with the other components of the body and should not show the exaggerations depicted in the Athletic Type of Kretchmer and Sigaud's Muscular Type.

The reactivity and sexuality of these individuals correspond to those considered normal.

The psychology is that embodied in the Greek term σωφροσύνη. It is characterised by well-balanced mental powers and an emotional tone without intense oscillations either towards intensity or towards apathy and depression.

The harmonious biotype cannot be described analytically and thus cannot be put on to paper, but every clinician with a general knowledge of humanity who has looked at patients and not only at their disease has in his mind this picture; although it is of course an abstract ideal creation—all biotypes are abstract creations—it helps him to assess the various constitutional types that deviate from this norm.

The Hypersthenic Biotypes.

The Hypertonic Hyperpituitary Biotype. One of the pioneers of the modern study of constitution, Tandler, used to divide human types into three; hypertonics, mesotonics and hypotonics, adding: "The hypertonics make history, the mesotonics submit to history, and the hypotonics write history." The basis of Tandler's classification, muscular tonus, can no longer be accepted, but the hypertonic biotype can easily be isolated from the motley human beings all around us, not, however, on the basis only of muscular tonus but of a general psychophysical biological tonus.

This biotype is also designated hyperpituitary, or more precisely hyperantepituitary. It is characterised biochemically by predominance of anabolism, particularly as regards proteins, and from the point of view of constitutional regulatory function by intensified function of the phyone and gonadal systems, the former being completely centred and the latter closely linked in the antepituitary.

Such individuals are tall, muscular, physically and mentally active. Their face is expressive, sometimes hard, the nose large, the chin projecting, the jaws are powerful and the teeth sometimes spaced. They may be bulky but

from muscle, not fat. They are definitely extravert and their activity is well directed. They are men of action, often of fighting disposition but not with the useless aggressiveness of certain adrenal hypertonics. They have ambition, drive, and an orderly intellect leaning more to the practical than to speculation. Sexually they are powerful.

In certain cases the head and extremities are large in proportion to the stature, composing an Acromegaloid Biotype as a form of the Hypertonic Biotype. This indicates increased reactivity of the small bones of the extremities and skull to growth hormone.

Individuals of Hypertonic Biotype are not usually long lived but their life is lived intensely. They are predisposed to hyperpituitary conditions but late in life they fall victims of hypopituitary diseases. Napoleon is a characteristic example of Hypertonic Biotype with termination in a state of hypopituitarism.

The Hypertensive-Adrenal Biotype. This is a hypersthenic biotype like the preceding one, but its physiological basis is principally a tendency to cortical or medullary adrenal hyperfunction. This colours the external manifestations.

Morphologically these individuals are pyknic, as described by Kretchmer, endomorphic as described by Sheldon, their body bulk being considerable and their body cavities—head, chest, stomach—well developed peripherally. They show medium height, a rounded figure, a soft broad face on a short massive neck. A fat paunch protrudes from the deep vaulted chest, which broadens out towards the lower part of the body. The limbs are soft and rounded, displaying little muscle or bone relief, the hands soft, short and wide, the shoulders rounded, often pushed downwards and inwards. The head sinks forward between the shoulders so that the thick short neck seems to disappear and the upper part of the spinal column takes on a kyphotic bend. There is a tendency to obesity, mostly restricted and localised on the trunk, face and abdomen but absent from hips and limbs. The skin is smooth, well fitting and of moderate thickness. This habitus is particularly typical between 30 and 44.

The temperament is cycloid, *i.e.,* characterised by alternation of elation and depression, but elation dominates. Such individuals are ambitious, inclined to assume unnecessary burdens and to take their responsibilities too seriously. They are often hot-headed, flare up all of a sudden and are soon tranquil again. They cannot halt behind a mountain. When anything gets in their way they see red at once and try to get what they want by force. They cannot swallow their indignation and preserve an equable exterior while intent on revenge, as this occurs in the Harmonious and the Hypertonic-Hyperpituitary, but manifest their feelings immediately in a hearty outburst. They then feel unburdened and a little tired and depressed.

These individuals are active, brisk, persistent and exacting. Their intelligence is above the average, and they are often perfectionists. On the whole, tension is the leitmotif of the psychology, not the aimless restlessness of the hyperthyroidean, not the well directed ambition and fighting spirit of the hyperpituitarian, but a tension originating in an inner instability which they

endeavour to mask by outward calm.

Sexually they are usually on the hypersthenic side. The blood pressure is in the high limits of the normal.

Such individuals are predisposed to cycloid psychoneuroses and psychoses, to hyperpiesia and coronary thrombosis. They are capable of doing well in any career but as they are usually directed towards those giving the best plums of life they often become " big business " men and politicians. They need much advice on restoring the balance and controlling the conduct of their life, however, and need careful watching from the medical point of view.

The Hyperthyroid Biotype. These are individuals who because of certain genetic factors are born into a constitutional type or biotype centred on the function of their thyrohormone system, manifesting throughout life their tendency to hyperfunction of this system.

They have a youthful appearance which they maintain up to an advanced age, although their hair is prematurely grey. Their build is slender, longilinear, they have thin fingers and toes with well-developed nails. The teeth are well developed. The facies, with its fair complexion, has a mobile, somewhat strained expression, and this, with the brilliant eyes, gives an impression of agility and activity.

These persons are highly strung, prone to external but not always well-directed activity. They live strenuously and are inclined to select the more difficult course with determination to succeed, but their activity shows a certain restlessness which distinguishes them from hypertonic hyperpituitarians, whose activity is ordered, and from hypertensive adrenals, in whom aggressiveness dominates. They depend solely on their own resources and do not even confide in others. They become tense, anxious and desperate, making excessive demands upon their body. Their activity is more cerebral. Intellectually they are characterised by rapid association of ideas but are unable to sustain a steady mental effort. They are bad sleepers.

They are very active but have phases of fatigue. They perspire easily and do not tolerate heat. The seaside upsets them but high altitudes are beneficial. The vasomotor system is unstable with a tendency to tachycardia on effort and after emotion. The lymphatic glands are hyperplastic. Sexuality is somewhat diminished.

The biochemical basis of this " type of life " is an intensified metabolism. The candle burns quickly.

Such biotypes are not suited to physical work but to mental activity without exaggerated sedentarity. They need fresh air and moderate exercise. They go through life feeling intensely its joys and sorrows and are used up before their time.

They are predisposed essentially to Graves' disease. This was pointed out in masterly fashion by Chvostek junior. In fact, there is little difference between this biotype and some formes frustes of Graves' disease. Despite some superficial morphological similarities with the habitus of tuberculous individuals, hyperthyroid biotypes do not appear to show any predisposition to

this disease. I have, however, noted this constitutional type in individuals suffering from depressive psychoses.

The Hypersensitive Biotype. Its physiological basis is not absolutely clear. An important element is a particular mode of function of the psycho-associational cortex component of the system of constitutional regulation, making for increased irritability of that component. Another element is a particular mode of function of the parathormone system making for depressive reactions of this system and thus for hypocalcæmia, which increases the general nervous irritability. The so-called " spasmophilic diathesis " is included in this biotypological picture. A third factor is a special mode of function of the neuro-vegetative system making for increased lability or irritability of this system, and in fact many of Eppinger and Hess' sympatheticotonics and vagotonics and Bergman's " vegetative stigmatisierte " belong to this constitutional biotype.

There is nothing notable in the morphological and sexual features of these individuals, although they are usually thin and longilinear and not very potent despite their sexual excitability. The characteristic features of this biotype bear essentially on the psychology and reactivity.

Psychologically they are hyperemotive. They vibrate intensely to all the joys and sorrows of life, and thus are either highly elated or deeply depressed according to circumstances. Their emotional reactions are violent and accompanied by physical symptoms such as sweating, tachycardia and vasomotor phenomena. A fine description of these mental factors was given by the French psychiatrist Ernest Dupré in his work on what he termed " emotive diathesis."

The reactivity of these individuals is essentially characteristic. In this sphere also they react intensely to all external stimuli. Jars or noises make them jump. A mild stimulation of their digestive organs or their nervous system causes fainting, spasms and even convulsions. The outstanding feature in marked cases, however, is the capacity to react by the so-called allergic manifestations—asthma, hay fever, urticaria, eczema and neurodermatous and other symptoms—to factors such as certain foodstuffs, dust, pollen and other elements completely innocuous to other individuals. The hypersensitivity is in the cells in general as well as in the brain.

The Hyposthenic Biotypes.

The Hypotonic-Hypopituitary Biotype. This is the converse of the hypertonic-hyperpituitary biotype. The term hypotonic is taken in the sense of general biological tone, although in this biotype the muscular tonus also is particularly diminished. This constitutional type is bound up with weak function of the phyone and gonadal systems. Its morbid exaggeration is represented by pituitary infantilism.

Morphologically the stature is diminished. Thinness is characteristic, such individuals being essentially " chetivistic." Limbs are short in relation to the trunk. Apart from the short stature the general structure is longilinear.

Flaccidity of the abdominal muscles and diminished trophicity of the various ligaments causes visceroptosis and great mobility of the joints.

Mentally, except in some cases with abnormal psychological reactions, they are on the depressive side. They are incapable of sustained mental effort and tire easily. Their intellect is good but somewhat speculative. They are good at artistic and poetical work but altogether do not achieve much. They have no drive, no ambition. They are introverts, centred on themselves, poor in emotional life.

Their general reactivity is characterised by chronic fatigue. For this reason they shun all physical effort and sports, and prefer to stay at home and read or write. Sexually they are weak.

The Eunuchoid Biotype. This represents a weak function of the adrenocortin and testosterone systems in males, the œstrin system in females. Biochemically protein and fat catabolism seems to predominate in these individuals.

The male eunuchoid biotype shows, morphologically, tallness, thinness and macroskelia. The span of these men is greater than their height, their lower segment (from pubis to the soles of the feet) is greater than the upper from pubis to the top of the head). They are typically longilinear, with a small head and receding chin. Their thinness is due to poor development of fat but also to the hypotrophy of their muscles, which are thin and flaccid. The flaccidity is marked in the abdominal muscles, and for this reason the abdomen bulges and falls (enteroptotic abdomen) and visceroptosis is the result. The ligaments also show some degree of flaccidity. Radiological investigation shows an elongated atonic stomach—many of the gastroptoses of bygone physicians were constitutional features of this biotype—and a "cœur en goutte." Feminine traits appear in the general habitus and gait.

Psychologically they are very sensitive and prone to introversion, a "schizoid" temperament, to use Kretchmer's expression. Their intellect is good but imitative. They are of artistic disposition. They show certain infantilistic traits and feminine mannerisms. They do not mature into virile men. Their introversion and tendency to live their own life may make them fanatics and sectarians. They are often very emotive.

Their general reactivity is characterised by an asthenic laziness and a tendency to avoid physical effort. Sexually they are weak, sometimes with a leaning to passive homosexuality. Organically they have a weak digestion.

Such individuals, with the addition of environmental factors, develop into a more complete eunuchoidism. Their gastroenteroptosis predisposes them to various digestive disturbances and duodenal ulcer (Draper's ulcer habitus corresponds to our eunuchoid biotype). They are predisposed also to tuberculosis of the lungs. As catabolism dominates in the metabolic features of these individuals they easily lose weight in the course of acute diseases and are very tired during convalescence, which is slow.

With additional factors they develop schizoid psychoses reaching real

schizophrenia. It seems also that acute poliomyelitis attacks such persons by preference.

The female Eunuchoid Biotype shows similar features. Menstruation is irregular, occurs late and is easily upset by emotion or disease. Hypersensitiveness is more accentuated than in the male, and infantilistic traits of emotional immaturity are more marked.

The Sluggish Thyro-Pituitary Biotype. The physiological basis of this biotype is a particular mode of function of the thyroid system, thyroid hypofunction. Often the fat-catabolic systems, mainly the pituitary, also are in hypofunction. In its general lines this biotype is in opposition to the hyperthyroid. The biochemical formula here is slowness of oxidation and metabolism in general, a metabolic stagnation corresponding to the physical and mental sluggishness.

Morphologically these persons are often below normal height and usually fat and infiltrated. Their facies is apathetic and dull, making apparent their slow cerebration and frequent mental depression. Head and thorax are large. The abdomen is gross and protruding. The hair is coarse, the teeth are prone to caries and fall easily. The skin is sallow, dirty, infiltrated and dry. The whole gives an impression of heaviness.

Psychologically slow cerebration dominates. They cannot concentrate and are incapable of any intellectual effort. Memory in particular is bad. As they are apathetic they are very conservative in their outlook and fear any innovation. As they do not understand much they are often anxious about trifles. They come repeatedly to the consulting-room with their anxiety but cannot explain their symptoms.

The reactivity is also characterised by the leitmotif of their constitutional type, sluggishness. Their movements are very slow. They take an almost interminable time to dress and undress. They perspire with difficulty and are very sensitive to cold. Sexually they are weak. The libido drive is deficient. Women have menstrual disturbances on the plus or minus side. Appetite is small, digestion slow, and constipation occurs easily.

Given certain additional factors they develop more distinct hypothyroidean diseases. These biotypological features are often found in patients suffering from eczema, acne and certain allergic manifestations.

The Intersexual Biotypes.

The intersexual biotypes are the male feministic and the female virilistic. The male feministic biotype is characterised by certain female morphological and psychological features, and the female virilistic by male morphological and psychological features.

Recognition of such biotypes helps us to understand many psychological disturbances. Certain diseases of the nervous system such as disseminated sclerosis occur either in virilistic women or in feministic men. Feminine traits frequently exist in men showing gall-bladder lithiasis (a woman's disease), and I have noticed the special efficacity of certain medicines acting principally

on women—such as the homœopathic ignatia—when administered to male feministic biotypes.

The Significance of Biotypology.

The reader must have recognised in most of these biotypes formes frustes of various endocrine-constitutional diseases described in this work. In fact, between biotypes and distinct cases of endocrine-constitutional diseases there is progressive gradation. Individuals born with a certain mode of function of their constitutional regulatory system accentuate that mode of function when subjected to the influence of certain environmental factors. Disease is not something separate from life but a manifestation of life. Disease is in us, by us, and we could add for many diseases, particularly psychoneuroses, for us. Not only disease but all other manifestations of life depend on our constitution. Our fate is our constitution.

It is not a fate against which we are powerless, however, and the much-neglected biotypology becomes the basis of modern preventive medicine. By correcting any abnormal deviations—and it is possible to do so—more serious conditions can be avoided. At the International Medical Week at Salsomaggiore in 1937 devoted to constitutional medicine and endocrinology, I proposed the creation of constitutional clinics as institutes of preventive medicine, clinics in which individuals would be examined according to the principles of biotypology particularly during the critical years of life—birth; seventh year, puberty, twenty-first year, forty-fiftieth years—the phases in which there are endocrine, or more precisely constitutional storms. Any abnormal deviation should be corrected, and thus not only would more severe constitutional diseases be avoided but also the individual would be rendered stronger to react to any adverse external influence, any other morbid etiological factor.

Thus biotypology crowns constitutional medicine, because prevention is the real object of our art and biotypology places constitutional medicine on the preventive plane. Thus we reach the ideal expressed by Hippocrates: "He is the best physician who can foresee and prevent."

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CHAPTERS LI and LII

THE ENDOCRINE AND CONSTITUTIONAL FACTORS IN DISEASE
BIOTYPOLOGY

I have developed the modern constitutional point of view in medicine in a series of publications dating from the first World War. (It was, in fact, on the Macedonian Front that I planned my first lectures on Constitutional or Neohippocratic Medicine, given at the Evangelismos Hospital of Athens immediately after the 1918 armistice.) My first publications are scattered in Greek medical papers of that period. My principal object in leaving Athens for London was to work on the constitutional idea in a wider circle.

The first work in which I developed the modern constitutional idea in England was "The Neohippocratic Theory as Basis of Contemporary Medical Thought and Practice," a paper read at the Annual Meeting of the International Society of Medical Hydrology in 1928 and published in the Archives of Medical Hydrology in the same year.

In my book, "The Modern Therapeutics of Internal Diseases, An Introduction to Medical Practice" (1931, *Bailliere, Tindall & Cox*) I developed this constitutional idea more extensively.

Immediately after the publication of this book I gave a lecture in Paris on Constitutional or Neohippocratic Medicine, after which a group of French physicians under the chairmanship of Professor Laignel-Lavastine founded the International Society of Neohippocratic Medicine. The First International Congress of Neohippocratism was held in Paris in 1937, and I was asked to deliver the introductory address. In the previous year I had developed the constitutional idea at the first conference on Constitutional Medicine based on Endocrinology in Salso-maggiore, under the presidency of N. Pende.

In 1937 my presidential address at the Section of History of the Royal Society of Medicine dealt with Neohippocratism (Proc. R.S.M., 1937, **31**).

Meantime I had published various papers on this subject, including " Recent Developments in Gastroenterology and Metabolism " (Med. World, 1933, January 6), " Physical Medicine in Contemporary Medical Practice " (Med. World, 1934, August 31 and September 7), " Education for Health according to the Principles of Modern Medicine " (New Ideals Quarterly, 1932, **6,** 171), " Neohippocratism and Homœopathy " (series of papers in Homéopathie Moderne and Mouvement Homéopathique, *Paris,* 1937), and an introductory paper on " Constitutional Medicine and Endocrinology " in " Constitutional Medicine " (1945, *Frèderick Muller*). The same trend of thought was followed in all my papers on more special nosographical subjects, including my book on " Diseases of the Intestines " (1927, *Bailliere, Tindall & Cox*).

I apologise for this long note on references to my personal work on the constitutional outlook, but as this view is now penetrating medical thought and practice I append it as a contribution to the history of contemporary medical thought.

My guiding principle since 1918 has been to set constitutional medicine on a precise scientific basis through study of metabolism, of the neuro-vegetative system and of endocrine function. This movement was of Mediterranean origin, arising simultaneously in Athens, Genoa and Madrid. Unfortunately, political reasons disrupted this new Mediterranean Medicine.

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APPENDIX TO BIBLIOGRAPHY OF CHAPTERS II AND III

THE HYPOTHALAMO-HYPOPHYSEAL CONNECTIONS

The conception of hypothalamo-hypophyseal connections which constitutes the most important general physiopathological principle underlying this work on Clinical Endocrinology, is gaining confirmation through recent work.

There is no need to refer to the many publications demonstrating, clinically and experimentally, these connections. The work cited in the physiological section of this book is amply confirmed, and it is sufficient to demonstrate the hypothalamo-hypophyseal (antehypophyseal and posthypophyseal) connections.

It is interesting to quote some histological work because this link seems to be weak, because although nerves have been described in both the anterior and posterior pituitary, authors have hesitated to assign to these nerves a physiological role.

The following work can be cited.

Roussy and Mossinger.

Dandy (Amer. J. Anat., 1913, **15,** 333) described nervous fibres in the anterior pituitary.

Pines (Ztschr. f. Psychol. u. Neurol., 1925, **32,** 8) found in the anterior lobe pericellular nerves terminating in button-like thickenings on the surface of the secretory cells.

Brooks and Gersh (Anat. Rec., 1938, **70,** 10) found a terminal net enclosing both acidophiles and basophiles of the hypophysis of the rat. In another paper (Endocrin., 1941, **28,** 1) they described fibres passing from the stalk and posterior lobe into the anterior lobe of both rat and rabbit.

Hair (Anat. Rec., 1937, **71,** 141) mentioned plentiful nerves in the anterior lobe.

Rasmussen (Endocrin., 1938, **33,** 263) also described numerous fibres in the anterior lobe coming from the cavernous plexus. These "become more and more scattered until nerve fibres may be seen on the vascular stroma between cell cords. Here and there a fibre may be woven in and out among the epithelial cells." Rasmussen considered these fibres as vasomotor but did not give any demonstration of his interpretation.

Truscott (J. Compar. Neurol., 1944, **80,** 235) reported a surprising number of fibres in the anterior lobe of the hypophysis of the rat, coming from the hypothalamus.

Drager (Endocrin., 1945, **37,** 124), in studying the Avian hypophysis, found nerve fibres only in the pars tuberalis, which is part of the anterior lobe. It is possible, according to this author, that these nerve terminations are sufficient to set up the secretory processes.

Among recent physiological work pointing to hypothalamo-hypophyseal connections the following may be cited.

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One of the interesting results is that a direct nervous hypothalamo-antehypophyseal tract is not considered as the only mechanism of hypothalamo-antehypophyseal connections. Secretory cells have been demonstrated in the hypothalamus, and these may secrete an acetylcholine-like hormone which acts on the anterior pituitary to stimulate its cells to secrete the various antepituitary hormones.

The quotation from Hoskins on the title page is taken from his paper "Progress and Problems in Endocrinology" (J. A. M. A., September 21, 1935). It is intersting to compare it with the quotation from Plato which appeared on the title page of my "Modern Therapeutics of Internal Diseases," "Good physicians apply their treatment to the whole body and attempt to heal the sick part or organ by treating the whole individual."

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